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GEORGIA INSTITUTE OF TECHNOLOGY
Office of Contract Administration

SPONSORED PROJECT INITIATION

Date: March 17, 1976

Project Title: Photochemical Synthesis of Sesquiterpenes

Project No: G-33-612

Project Director: Dr. Drury S. Caine, III

Sponsor: Public Health Service, NIH

Agreement Period: From 5/1/76 Until 4/30/77

Type Agreement: Grant No. 5 R01 CA12193-09

Amount: $52,101 PHS
5,441 GIT (Cost Sharing G-33-370)
$57,542 Total

Reports Required: Interim Progress
Terminal Progress

Sponsor Contact Person(s):

Technical Matters	Contractual Matters (thru OCA)
Dr. M. V. Nadkarni	Mr. Joseph Fitzgerald
Division of Cancer Research Resources and Centers	Division of Cancer Research Resources and Centers
National Cancer Institute	National Cancer Institute
Public Health Service	Public Health Service
Bethesda, Maryland 20014	Bethesda, Maryland 20014

NOTE: Continuation of G-33-677

Assigned to: Chemistry (School/Laboratory) (301) 496-7296

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- Other _____

CA-3 (3/76)

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GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION

Date: 4/11/78

Project Title: Photochemical Synthesis of Sesquiterpenes

Project No: G-33-612

Project Director: Dr. Drury S. Caine, III

Sponsor: DHEW/PHS/NIH National Cancer Institute

Effective Termination Date: 4/30/77 (End 09 Budget Period)

Clearance of Accounting Charges: n/a - all have cleared

Grant/Contract Closeout Actions Remaining: None

_ Final Invoice and Closing Documents
_ Final Fiscal Report
_ Final Report of Inventions
_ Govt. Property Inventory & Related Certificate
_ Classified Material Certificate
_ Other _____

Assigned to: Chemistry (School/Laboratory)

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CA—4 (3/76)

G-33-612

THE PHOTOCHEMICAL TOTAL SYNTHESIS OF (±)-3-OXO-α-CADINOL AND (±)-α-CADINOL[1]

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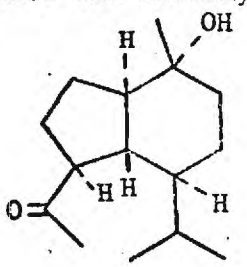
School of Chemistry, Georgia Institute of Technology
Atlanta, Georgia 30332

In a recently reported total synthesis of the sesquiterpene (±)-oplopanone (1) we utilized chemical rearrangement of the 6/5-fused 4-methoxy dienone 2a to prepare the 5/6-fused acetoxy 3a which was readily transformed into the natural product.[2] We now wish to report the total esis of the cadinane derivatives (±)-3-oxo-α-cadinol (4a)[3] and (±)-α-cadinol (4b)[4] by a sequ- which utilizes photochemical rearrangement of the bicyclic dienone 2b in glacial acetic acid oduce the acetoxy enone 3b followed by expansion of the A ring.



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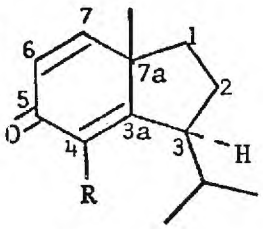
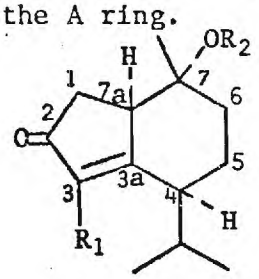
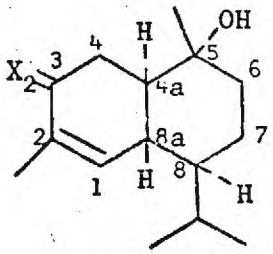


2a. R=OCH$_3$
b. R=H



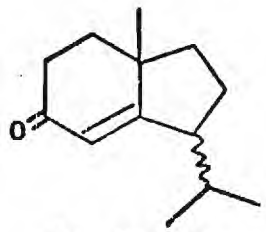
3a. R$_1$=OCH$_3$, R$_2$=Ac
b. R$_1$=H, R$_2$=Ac
c. R$_1$= R$_2$=H



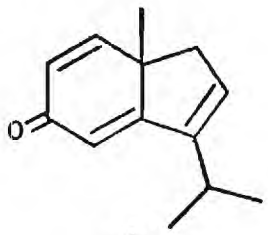
4a. X$_2$=O
b. X$_2$=H$_2$

The bicyclic enone 5a which has a cis relationship of the angular methyl group and the isopropyl was synthesized in a highly stereoselective manner for use as a precursor to the dienone 2b. 60:40 mixture of 5a[5] [bp 94°(0.10mm); uv max (95% EtOH) 241 nm (ε 13,400); ir (CCl_4) 1667 unsatd. C=O) and 1632 cm^{-1} (conjd. C=C); nmr (CCl_4) δ0.90 and 1.01 (pair of d's, J = 6.5 Hz, 3β-CH_3CHCH_3), 1.17 (s, 3 H, 7a-CH_3), and 5.67 ppm (d, J = 2 Hz, 1 H, 4-H)] and the corresponding isomer 5b[5] [ir (CCl_4) 1670 (α,β-unsatd. C=O) and 1634 cm^{-1} (conjd. C=C); nmr (CCl_4); and 1.01 (pair of d's, J = 6.5 Hz, 6 H, 3α-CH_3CHCH_3), 1.18 (s, 3 H, 7a-CH_3), and 5.60 ppm = 2 Hz, 1 H, 4-H)] was obtained in 77% yield by Michael addition of 2-methyl-5-isopropyl- pentanone[2,6] to methyl vinyl ketone (0.2 equiv KOH-C_2H_5OH, ether, 0°, 4 h) followed by aldol zation of the diketone intermediate (10% KOH-C_2H_5OH, reflux, 2 h). Separation of 5a and 5b ifficult because of the extreme ease of epimerization of these compounds, but partial separation be affected by low pressure chromatography on a pre-packed silica gel column. Pure samples and 5b were finally obtained by preparative GLC.[7] Appropriate equilibration studies revealed the aldol cyclization conditions yielded the thermodynamic mixture of isomers. Levisalles and kers[8] have reported the degradation of (-)-carotol into the cis enone 5a (actually, the iomer of opposite absolute configuration to that shown in 5a) and further conversion of this und into the corresponding trans isomer by acid treatment. They suggested that the trans

stable isomer was obtained by oxidation (2.2 equiv DDQ, dioxane, reflux, 3.5 h) of the thermomic mixture of enones to the trienone 6[5] [44% yield; mp 55.9-56.9°; uv max (95% EtOH) 225 nm ,400), 248 (7,200), and 308 (9,600); ir (CCl_4) 1652 (α,β-unsatd. C=O), 1626 and 1594 cm^{-1} jd. C=C); nmr (CCl_4) δ 1.13 and 1.20 (pair of d's, J = 6.5 Hz, 6 H, 3-CH_3CHCH_3), 1.35 (s, 3 H, H_3), 6.00 (d, J = 1.5 Hz, 1 H, 4-H), 6.03 (d of d, J = 1.5 and 10 Hz, 1 H, 6-H), 6.17 (m, 1 H, , and 7.10 ppm (d, J = 10 Hz, 1 H, 7-H)] followed by selective reduction (5% Pd (C), cyclohexene. OH, reflux, 2.5 h) of the γ,δ-double bond and the disubstituted double bond in the A ring by sfer hydrogenation.[9] The latter reaction yielded essentially quantitatively a mixture contain->95% 5a and a trace of 5b. It was expected that addition of hydrogen to the γ,δ-double bond would occur largely from the side of the molecule opposite the angular methyl group to give cis isomer 5a - the major product in the equilibrium mixture. The subsequent work supported premise.



5a. β-i-Pr
b. α-i-Pr



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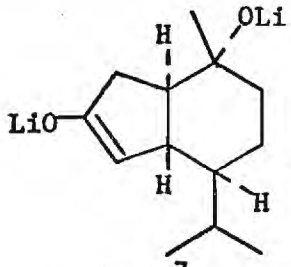

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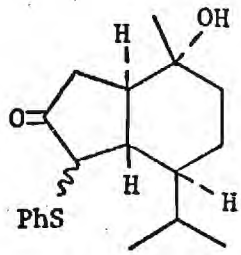
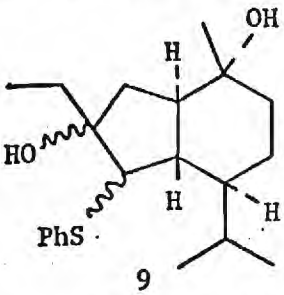


8a. β-SPh
b. α-SPh

Enone 5a was converted into dienone 2b[5] [bp 74°(0.05 mm); uv max (95% EtOH) 240 nm (ε 13,800); CCl_4) 1663 (α,β-unsatd. C=O), 1635 and 1607 cm^{-1} (conjd. C=C); nmr (CCl_4) δ 0.98 and 1.05 (pair 's, J = 6.5 Hz, 6 H, 3β-CH_3CHCH_3), 1.23 (s, 3 H, 7a-CH_3), 5.97 (d, J = 1.5 Hz, 1 H, 4-H), 6.02 f d, J = 1.5 and 10 Hz, 1 H, 6-H), and 6.98 ppm (d, J = 10 Hz, 1 H, 7-H)] in 75% yield by kineti otonation (1.1 equiv LDA, THF, -70°) to form the homoannular lithium dienolate,[10] trapping of the ate with phenylselenenyl bromide[11a] (1.1 equiv PhSeBr, THF, -70°), and oxidation - elimination he selenoxide[11a,b] (2 equiv H_2O_2, H_2O, CH_2Cl_2, 25°, 15 min).

Irradiation of a 1% solution of 2b in glacial acetic acid (450- watt Hanovia high pressure amp, quartz probe, 30 min) yielded the acetoxy enone 3b[5] [40% yield; mp 100.2-101.2°; uv max EtOH) 231 nm (ε 15,700); ir (CCl_4) 1738 (OAc), 1716 (α,β-unsatd. C=O), and 1684 cm^{-1} (conjd. ; nmr (CCl_4) δ0.95 and 1.03 (pair of d's, J = 6.5 Hz, 6 H, 4β-CH_3CHCH_3), 1.20 (s, 3 H, 7-CH_3), (s, 3 H, 7-OAc), 2.22 (d, J = 4.5 Hz, 2 H, 1-CH_2), 3.27 (t, J = 4.5 Hz, 1 H, 7a-H), and 5.82 (br s, 1 H, 3-H)] which had the proper stereochemistry at three of the four chiral centers ent in the target cadinane derivatives.[12] It was expected that the enolate alkoxide 7 could enerated regiospecifically by lithium-ammonia reduction[13] of enone 3b and trapped with a henylating agent[14] to produce the 3-phenylthio ketones 8. Then, by application of the recently rted alkylative-oxidative ring expansion procedure of Trost and Hiori,[15] 8 should be convertible (±)-3-oxo-α-cadinol. However, attempted lithium-ammonia reduction of 3b was found to be panied by extensive reductive cleavage of the tertiary acetoxy group. Therefore, prior to tion 3b was converted into the hydroxy enone 3c[5,16] [95% yield; mp 110.5-111.5°; uv max (95% 235 nm (ε 13,500); ir (CCl_4) 3600 and 3400 (OH), 1714 (α,β-unsatd. C=O), and 1682 cm^{-1} (conjd. nmr ($CDCl_3$) δ0.93 and 1.03 (pair of d's, J = 6.5 Hz, 6 H, 4β-CH_3CHCH_3), 0.98 (s, 3 H, 7-CH_3),

eduction (2 equiv LAH, ether, reflux, 1.5 h) of both the saturated carbonyl group and the ester tion followed by Jones oxidation of the secondary allylic alcohol. Enone 3c was then subjected ithium-ammonia reduction (2.5 g.at. Li, NH_3-THF, -33°, 1.25 h); the excess lithium was destroyed sodium benzoate, and the ammonia was allowed to evaporate at atmospheric pressure and finally ved completely under vacuum (<1 mm, 50°). The solid enolate alkoxide 7 was then dissolved in drous THF and the solution was cooled to -70° and treated first with 1.1 equiv of LDA[17] in hexane followed by diphenyldisulfide (3.5 equiv, -70° ⟶ 25°, 2.5 h). Workup gave a 1:3 mixture he 3-phenylthio ketones 8a[5] [19% yield; mp 138.5-139.0°; uv max (95% EtOH) 212 nm (ε 8,700 as a lder), 250 (5,000), and 306 (380); ir (CCl_4) 3600 and 3420 (OH), 1748 (C=O), and 1581 cm^{-1} matic C=C); nmr ($CDCl_3$) δ 0.90 and 0.93 (pair of d's, J = 7 Hz, 6 H; 4β-CH_3CHCH_3), 1.10 (s, 3 H, $_3$), 3.17 (br d, J = 8 Hz, 1 H, 3α-H), and 7.20-7.63 ppm (m, 5 H, β-SPh)] and 8b[5] [57% yield; mp 5-112.5°; uv max (95% EtOH) 219 nm (ε 8,000), 242 (4,200 as a shoulder), and 312 (910); ir $_4$) 3600 and 3420 (OH), 1739 (C=O), and 1584 cm^{-1} (aromatic C=C); nmr ($CDCl_3$) δ0.82 and 0.92 r of d's, J = 7 Hz, 6 H, 4β-CH_3CHCH_3), 1.15 (s, 3 H, 7-CH_3), 3.58 (d, J = 4 Hz, 1 H, 3β-H), and -7.63 ppm (m, 5 H, α-SPh)] which were isolated by chromatography on florisil. These isomers independently converted into the same equilibrium mixture (35% 8a: 65% 8b) upon mild base treat-. Examination of the configurations of possible β carbanionic intermediates in the lithium-nia reduction[14] suggested that the trans-fused enolate should be obtained. This stereochemistry ell as the regiospecificity of the sulfenylation reaction was confirmed by a single crystal X-ray cture on the minor isomer 8a.[18]



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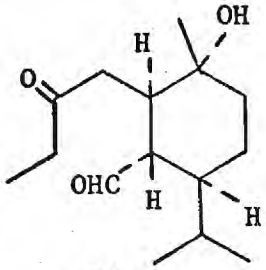

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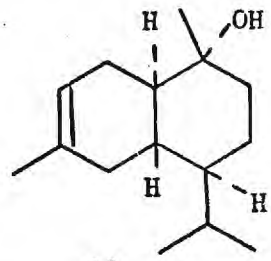

11

Addition of ethyllithium (3 equiv C_2H_5Li, ether-THF; 3 equiv HOAc; 4 equiv C_2H_5Li, -70° ⟶ 25°, h) to the 3α-phenylthio ketone 8b gave a mixture of isomeric phenylthio alcohols 9. Without fication, this material was oxidized (2 equiv $Pb(OAc)_4$, toluene-HOAc, 0°, 5 h) and hydrolyzed quiv $HgCl_2$, CH_3CN-H_2O, reflux, 4 h) to give a single product having spectral properties consist-with the keto aldehyde structure 10. Aldol cyclization (5% KOH-CH_3OH, reflux, 2 h) of this rmediate gave (±)-3-oxo-α-cadinol (4a)[5,19] [mp 111.5-111.8°; uv max (95% EtOH) 237 nm (ε 9,800); CCl_4) 3400 (OH), 1681 (α,β-unsatd. C=O), and 1649 cm^{-1} (conjd. C=C); nmr ($CDCl_3$) δ 0.83 and 0.98 ir of d's, J = 7 Hz, 6 H, 8β-CH_3CHCH_3), 1.17 (s, 3 H, 5-CH_3), 1.78 (br s 3 H, 2-CH_3), and 6.83 (br s $W_{1/2}$ = 4 Hz, 1 H, 1-H)] in 52% yield (from 8b) after chromatography on florisil. Wolff-Kishner reduction[20] (N_2H_4, C_2H_5OH-py, reflux, 15 h, $(CH_3)_3COK$, $C_6H_5CH_3$, reflux, 6 h) of ave a 2:1 mixture of unsaturated alcohols in 94% yield. These compounds were isolated by prepar GLC[7] and the major product (a colorless oil) proved to be (±)-α-cadinol (4b). It showed ir[21,] mr[22] spectal properties essentially identical to those previously reported for (-)-α-cadinol. lso gave a p-nitrobenzoate derivative[5] (mp 164-165°) having identical spectral (ir, nmr, ms) LC properties to those of an authentic sample of (-)-α-cadinol-p-nitrobenzoate.[23] The minor r from the reduction was assigned structure 11 [mp 91.0-91.9°, ir (CCl_4) 3600 and 3400 (OH),

(pair of d's, J = 7 Hz, 6 H, 8β-CH_3CHCH_3), 1.03 (s, 3 H, 5-CH_3), 1.60 (br s, 3 H, 2-CH_3), and ppm (br d, J = 5 Hz, 1 H, 3-H] on the basis of its spectral properties.

References and Notes

This investigation was supported by Public Health Service Grant No. CA 12193 from the National Cancer Institute.

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V. Herout and V. Sykora, Tetrahedron, 4, 246 (1958).

Correct exact mass data and/or elemental analyses have been obtained for all compounds for whic spectral data are reported.

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A 10 ft. x 1/4 in. stainless steel column containing 20% Carbowax K-20M on Chromosorb W HMDS was employed.

M. Allard, J. Levisalles, and H. Rudler, Bull. Soc. Chem. France, 303 (1968).

D. Burn, D. N. Kirk, and V. Petrow, Tetrahedron, 21, 1619 (1965).

R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, Tetrahedron Lett., 965 (1973).

a. H. J. Reich, J. M. Renga, and I. L. Reich, J. Amer. Chem. Soc., 97, 5434 (1975). See also b. K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, ibid., 95, 6137 (1973) and D. L. J. Clive, Chem. Comm., 695 (1973).

A conjugated dienone formally derived form elimination of acetic acid from 3b was also isolated in about 20% yield from the photolysis. However, no tricyclic product of the type obtained on photolysis of the model dienone containing no isopropyl substituent was observed. (See D. Caine, J. T. Gupton III, K. Ming, and W. J. Powers III, Chem. Commun., 469 (1973)).

For a review see D. Caine, Org. React., 23, 1 (1975).

B. M. Trost, T. N. Salzmann, and K. Hiroi, J. Amer. Chem. Soc., 98, 4887 (1976).

B. M. Trost and K. Hiroi, J. Amer. Chem. Soc., 97, 6911 (1975).

Hydroxy enone 3c could be obtained directly but in very low yield by irradiation of 2b in 45% aqueous acetic acid.

See ref. 14 for the role of a second equiv of strong base in sulfenylations at secondary center

The details of the X-ray crystallographic structure of 8a will be published later in a full paper. We are grateful to Professor J. A. Bertrand, Dr. H. Deutsch, and Dr. D. Van Deever of carrying out this determination.

The nmr spectral properties of 4a differ slightly from those reported for the natural product (ref. 3). Since neither a sample of authentic 4a nor its nmr spectrum were available to us, we are unable to explain this discrepancy.

M. F. Grundon, H. B. Henbest, and M. D. Scott, J. Chem. Soc., 1855 (1963).

We are grateful to Professor V. Herout for a copy of the ir spectrum of (-)-α-cadinol.

L. H. Briggs and G. W. White, Tetrahedron, 31, 1311 (1975).

We are grateful to Professor R. C. Cambie for supplying us with an authenic sample of (-)-α-cadinol p-nitrobenzoate prepared by the late Professor L. H. Briggs.

Revised

Photochemical Rearrangements of Cross-Conjugated Cyclohexadienones Related to Epimaalienone[1]

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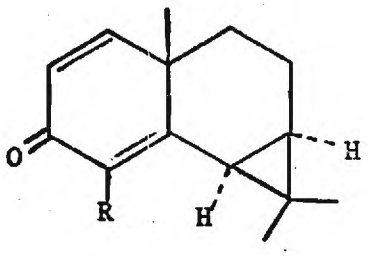
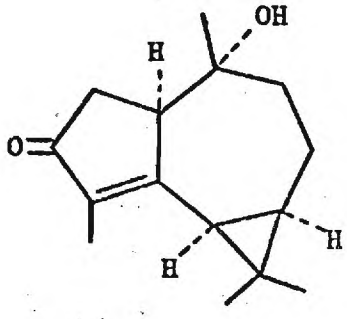
School of Chemistry

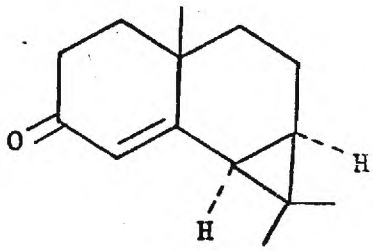
Georgia Institute of Technology

Atlanta, Georgia 30332

Recently, we reported that the tricyclic cross-conjugated cyclohexadienone 1a, derived from epimaalienone, was photochemically converted into the tricyclic hydroxy enone 2 on irradiation in aqueous acetic acid[2]. Compound 2 was utilized in a synthesis of (-)-4-epiglobulol and (+)-4-epiaromadendrene[2]. Since examples of successful photochemical rearrangements of cross-conjugated cyclohexadienones containing a conjugated cyclopropane ring are rare[3,4], further investigation of the photochemistry of compounds of the type 1 appeared to be of interest. In this paper we wish to report the results of irradiation of 1a in the aprotic solvent dioxane and of the irradiation of the related ring A unsubstituted dienone 1b in both dioxane and glacial acetic acid.







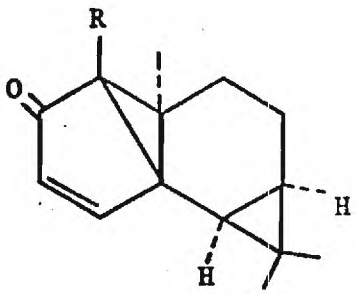
1a R = CH_3
1b R = H

2 3

The synthetic route employed for the preparation of 1b was similar to that used for the synthesis of 1a[2,5] except that the phenylselenenylation-selenoxide elimination procedure[6], involving conversion of the enone 3 to the homoannular lithium dienolate with lithium diisopropylamide (LDA) in THF at -70°[7], was used instead of oxidation with DDQ in dioxane.

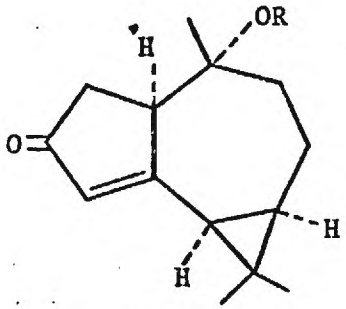
Irradiation of a dilute solution of 1a in anhydrous dioxane using a 2537 Å light source for 2.7 h at room temperature led to the formation of a single photoproduct which was isolated in 52% yield after column chromatography on silica gel. The spectral properties of this compound (see Experiment Section)

were completely consistent with the tetracyclic enone structure 4a. Under similar conditions irradiation of dienone 1b for 9.0 h produced a single photoproduct having spectral properties consistent with the structure 4b in 60% yield (based upon unrecovered starting material)[8].



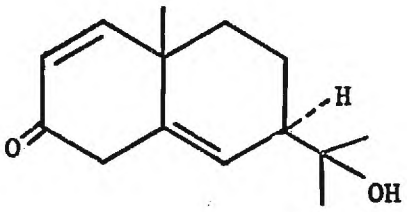
4a R = CH_3

4b R = H



5a R = H

5b R = $-\overset{O}{\overset{\|}{C}}-CH_3$



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Irradiation of 1b in 45% aqueous acetic acid gave erratic results. A compound having spectral properties, consistent with the hydroxy enone 5a was apparently formed in low yield in some runs, but in others the nmr and ir spectral properties of the photolysis mixture indicated that the major component had the ring-opened structure 6. Compound 6 was isolated by chromatography when a dilute solution of 1b was allowed to stand in 45% aqueous acetic acid in the dark for 1.0 h. Apparently, in aqueous acetic acid, 1,6 addition of water to the vinylogous cyclopropyl ketone system in 1b is an especially favorable process which largely prevents photochemical rearrangement of the dieneone. The inconsistent results obtained during irradiation of 1b were presumably related to variations in time between dissolution of the sample and the start of the irradiation period.

The structural assignment for 6 is based upon its nmr spectral and chemical properties (see Experimental Section).

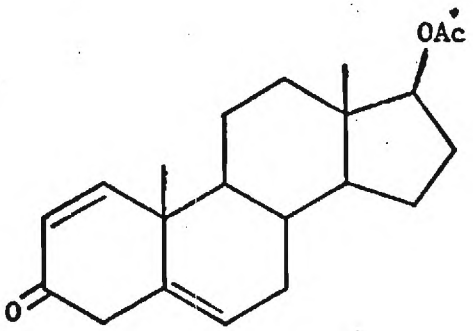
The absorption pattern for the methylene protons at C-4 was similar to that observed for the deconjugated steroidal dienone 7[9]. The lower field absorption at 3.18 δ was expected to be due to the axial (4β) proton and this was strongly supported by a deuterium exchange experiment. Thus, when 6 was mixed with 0.01 equivalent of NaOD in acetone-D_6/D_2O, the peak at 3.18 rapidly disappeared whereas the absorption at 2.82 δ simply changed from a doublet to a broad singlet. Axial protons α to ketones generally exchange much faster than equatorial protons[10].

The deconjugated dienone 6 was converted to conjugated dienone 8 on treatment with methanolic sodium hydroxide. The structural assignment for 8 followed readily from the close similarity of its nmr and ir spectral properties to those of related cross-conjugated dienones, e.g., 1b.

When dienone 1a was treated with aqueous acetic acid under similar conditions to those described for 1b, its slow conversion into a product apparently related to 6 was observed. However, the rate of this reaction was much too slow for it to be competitive with the normal dienone photochemical rearrangement.

Photochemical rearrangement of 1b could readily be accomplished using

glacial rather than aqueous acetic acid as the solvent. Thus the acetoxy enone 5b was produced in 71% yield when a dilute solution of 1b in glacial acetic acid was irradiated for 0.75 h using ultraviolet light with a wavelength greater than 3000 Å. No other products were isolated from the photolysis.



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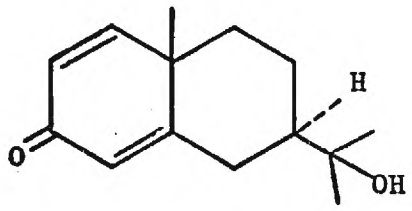
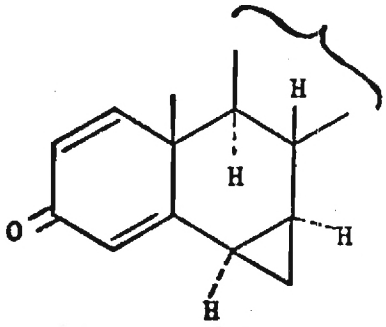


8

These results show that the predominate modes of photochemical rearrangement of dienones of the type 1 parallel those which are commonly observed for related systems in which the cyclopropane ring is absent[11]. The steroid derivative O-acetyl-1-dehydro-6β,7β-methylenetestosterone (9) which like 1 has a cis relationship of the cyclopropane ring and the angular methyl group has been reported to be readily converted into the bicyclohexenone derivative 10 on irradiation in dioxane at 2537 Å[4]. The photolability of dienones of the type 1 and 9 is in marked contrast to that of the isomeric systems 11 and 12, respectively, which have a trans relationship of the cyclopropane ring and the angular methyl substituent. For example, dienone 11a has been found to be stable to direct irradiation in aprotic[12] and protic media[3,13] while 12 was shown to be unchanged on irradiation in dioxane[4].

It has been suggested[11c] that the conversion of 9 into 10 proceeds via the generally accepted zwitterionic intermediate 13 which would have a trans relationship of the adjacent cyclopropane rings on the six-membered B ring. The failure of 12 to undergo an analogous rearrangement was attributed to the fact that the zwitterionic intermediate corresponding to 13 would be highly strained because the two adjacent cyclopropane rings on the six-membered B ring would have a cis relationship to each other. A similar explanation could account for the photostability of 11a. However, it is not obvious that the strain associated with adjacent cis cyclopropane rings would be of such magnitude as to preclude the formation of an intermediate related to 13. We have shown that the 2-carboxy dienone 11b undergoes rearrangement to 5/7-fused products having the cyclopropane ring intact on irradiation in dioxane and aqueous acetic acid[3,14]. However, whether the presence of the carboxyl group in some way provides stabilization of the zwitterionic intermediate derived from 11b or allows an alternative rearrangement pathway to intervene is not clear.

The photochemical behavior of 1a and 1b may be explained in terms of the zwitterionic intermediate 14 which is analogous to 13 derived from the steroidal system[15]. In dioxane the usual symmetry-allowed 1,4-sigmatropic rearrangement can lead to products of the type 4, while in aqueous or glacial acetic acid protonation of 14 on oxygen followed by solvolytic cleavage of the 5,10-bond would lead to fused-ring products such as 2 or 5. Normally, ring A unsubstituted dienones yield mixtures of fused-ring and spirocyclic products because solvolytic cleavage of both bonds of the cyclopropane ring of the mesoionic intermediate derived from protonation of 14 is possible. However, in the case of 14 topside attack of solvent



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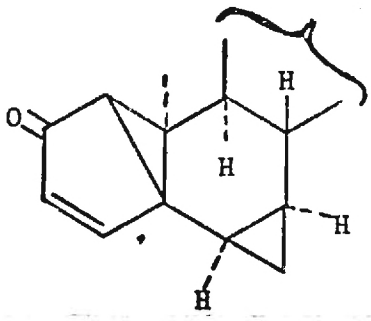

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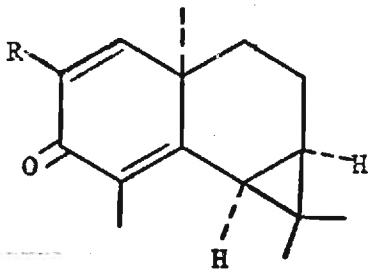
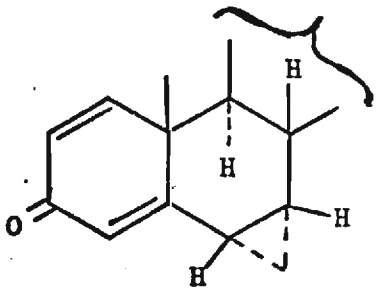


11a R = H

11b R = CO_2H



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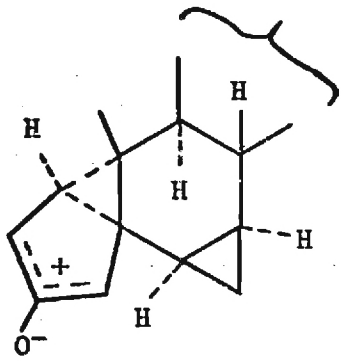

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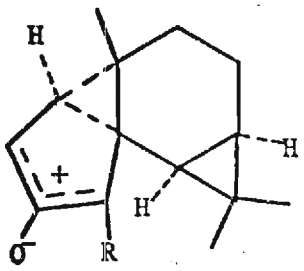
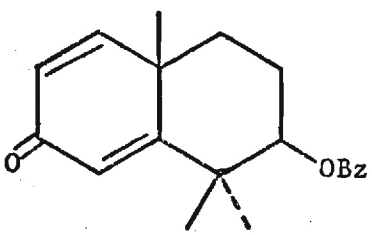


14a R = CH_3

14b R = H



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at C-10, which would lead to a spirocyclic hydroxy ketone, is hindered by the dimethylcyclopropane ring[16]. A similar steric argument has been used to account for the fact that a spirocyclic hydroxy ketone was not produced on irradiation of the ring A unsubstituted dienone 15[17].

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 457 instrument; nmr spectra were obtained using a Varian Assc. Model T-60 spectrometer; ultraviolet spectra were measured using a Beckman Model 25 instrument. Mass spectra were determined with a Hitachi Perkin-Elmer RMV-7 or a Varian Model M-66 spectrometer. Combustion analyses were performed by Atlantic Microlabs, Inc., Atlanta, Georgia.

For column chromatography either florisil (Fisher Scientific Co.) or silica gel (Grace, 60-200 mesh; deactivated with acetone before use) were employed as adsorbants.

A Hanovia 450-watt high pressure mercury lamp housed in a pyrex probe was used for the irradiation in acetic acid. A Hanau NK 20 seven-watt low pressure mercury lamp was used for all irradiations in dioxane. When either solvent was used, dry nitrogen was bubbled through the reaction vessel for a few minutes preceeding and during the period of irradiation.

Preparation of 4-normethyl-1,2-dehydroepimaalienone (1b). (-)-2-Carone was reacted with methyl vinyl ketone according to the procedure of Caine and Gupton[5]. The product (-)-3-(2-butanone-4-yl)-2-carone (bp 100-135° @ 0.30 mm) was obtained in 64% yield, and showed uv λ_{max} (95% EtOH) 220 nm

(ε 3,540); ir (CCl_4) 1720 and 1690 cm^{-1}; nmr δ_{TMS} (CCl_4) 0.85 (s, 3 H), 1.05 (s, 3 H), 1.15 (s, 3 H), and 2.10 ppm (s, 3 H); m/e (70 eV) 222.161 (EMC = 222.162).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.51; H, 9.96.

The product of the previous reaction (23.25 g, 0.105 m) was added dropwise to 200 ml of anhydrous saturated ethanolic hydrogen chloride at 5°. After warming to room temperature and stirring for 30 min, the reaction mixture was poured into 200 ml of ice-water and extracted with $CHCl_3$. Removal of solvent gave 24.0 g (95%) of cis-6-(2-chloropropane-2-yl)-3-keto-9-methyl-Δ^4-octahydronaphthalene mp 106-107° (from hexane); ir (CCl_4) 1675 and 1620 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.25 (s, 3 H), 1.60 (s, 6 H), and 5.65 ppm (broad s, 1 H); m/e (70 eV) 204 (M^+-HCl).

Anal. Calcd. for $C_{14}H_{21}OCl$: C, 69.84; H, 8.79. Found: C, 69.72; H, 8.80.

To a suspension of 10.7 g (ca 0.25 m) of sodium hydride in 50 ml dry dimethoxyethane (DME) was added 23.25 g (0.105 m) of the above chloro-enone in 500 ml of dry DME. The mixture was heated at reflux overnight, and 25 ml of ethanol was added. Removal of solvents and partitioning between ether and water followed by distillation yielded 11.8 g (68%) of an amber oil, 3: (bp 109-119° @ 0.08 mm); uv λ_{max} (95% EtOH) 277 nm (ε 18,200); ir (CCl_4) 1663 and 1592 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.10 (s, 3 H), 1.16 (s, 3 H), 1.20 (s, 3 H), and 5.86 ppm (s, 1 H); m/e (70 eV) 204.151 (EMC = 204.151).

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.10; H, 9.88.

Although compound 3 could be converted to 1b by DDQ oxidation, as reported for 1a[2], the yields were erratic and low. In the preferred method, 5.00 g (0.0245 m) of 3 in 25 ml of dry THF, was added slowly to 1.2 equiv of lithium diisopropylamide (LDA) in 100 ml of THF in a dry ice-acetone bath.

After stirring for an additional 30 min at this temperature, a solution prepared from 4.59 g (0.0147 m, 1.2 equiv) of diphenyldiselenide and 0.76 ml (2.35 g, 0.0147 m) of bromine in 25 ml of THF, was added quickly and the reaction mixture allowed to warm to room temperature. The crude phenylselenide was isolated and dissolved in 75 ml of methylene chloride. To this solution was added, over a 20 min period, 6.66 g (0.0588 m, 2.4 equiv) of 30% aqueous hydrogen peroxide dissolved in 20 ml of water. Slight external cooling was necessary to maintain the temperature at 25°. Extraction of the methylene chloride layer with aqueous $NaHCO_3$ and removal of the solvent yielded 5.1 g of yellow oil. Chromatography on florisil (20% ether in hexane) afforded 3.00 g (60%) of the crystalline dienone 1b: mp 87-88° (from pentane); uv λ_{max} (95% EtOH) 243 (ε 10,000) and 303 nm (ε 8600); ir (CCl_4) 1660, 1622 and 1588 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.18 (s, 6 H), 1.25 (s, 3 H), 5.95 (q, J = 1.5 and 10 Hz, 1 H), 6.13 (broad, J ≅ 1.5 Hz, 1 H) and 6.72 ppm (d, J = 10 Hz, 1 H); m/e (70 eV) 202.139 (EMC = 202.136).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.02; H, 8.99.

Irradiation of 1b in Dioxane. A 375 mg sample of dieneone 1b was dissolved in 100 ml of dry dioxane and irradiated for 9.0 h. The solvent was removed under reduced pressure and the crude material chromatographed on florisil. Elution with 10% ether in hexane afforded 133 mg (60%, based on unrecovered starting material) of 4b: mp 58-60° (from pentane); ir (CCl_4) 1700 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.07 (s, 6 H), 1.20 (s, 3 H), 5.78 (d, J = 6 Hz, 1 H) and 7.37 ppm (d, J = 6 Hz, 1 H).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.09; H, 8.97.

Further elution with 50% ether in hexane afforded 149 mg of starting material.

Irradiation of 1a in Dioxane. A solution of 516 mg of 1a was irradiated for 2.7 h in 100 ml of dry dioxane. After removal of solvent the residue was chromatographed on silica gel. Elution with hexane yielded 267 mg (52%) of 4a: bp 78-105° (bath temperature) @ 0.05 mm; uv λ_{max} (95% EtOH) 220 (ε 5450); and 280 nm (ε 2490); ir (CCl_4) 1695 and 1651 cm^{-1}; nmr δ_{TMS} (CCl_4), 0.98 (s, 3 H), 1.03 (s, 3 H), 1.12 (s, 3 H), 1.38 (s, 3 H), 5.84 (d, J = 6 Hz, 1 H) and 7.34 ppm (d, J = 6 Hz, 1 H); m/e (70 eV) 216.155 (EMC = 216.151).

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.09; H, 9.40.

Reaction of 1b with aqueous acetic acid. A solution of 100 mg (0.495 mm) of 1b in 10 ml of 45% aqueous acetic acid was allowed to stand for 1.0 h. The reaction mixture was poured into excess aqueous sodium bicarbonate and extracted with 50 ml of ether. After drying and solvent removal, approximately 110 mg (101%) of yellow oil was isolated. After chromatography on florisil (60% ether in hexane) 100 mg (92%) of 6 was isolated and showed the following properties: mp 75-76° (from ether-pentane); ir (CCl_4) 3310, 2970, 2920, 2860, 1678, and 1615 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.02 (s, 3 H), 1.10 (s, 3 H), 1.21 (s, 3 H), 2.82 (d, J = 17 Hz, 1 H), 3.18 (d, each member split into a triplet, J = 17 and 2.5 Hz, 1 H), 5.50 (broad s, 1 H), 5.70 (d, J = 10 Hz, 1 H) and 6.50 ppm (d, J = 10 Hz, 1 H).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.30; H, 9.17.

Irradiation of the signal at 5.50 δ changed the absorption at 3.18 δ into a doublet, each member of which was split into a doublet (J = 17 and 2.5 Hz). Irradiation at 2.25 δ produced the same effect on the signal at 3.18 δ as did irradiation at 5.50 δ.

When a solution of ca 100 mg of 6 in 0.5 ml of acetone-D_6 containing 0.01 equiv of NaOD and 0.10 ml D_2O was allowed to stand for ca 15 min the

following changes in the nmr spectrum were observed: the signal at 3.18 δ disappeared, whereas the one at 2.82 δ changed from a doublet to a broad singlet; the signal at 5.50 δ became much sharper and appeared as a doublet (J ≅ 2 Hz). When ca 100 mg of 6 was treated with excess NaOH in methanol a mixture of compounds (77 mg) could be isolated. Chromatography on florisil (75% ether in hexane) yielded 40 mg of a pale yellow oil, tentatively identified as 8: ir (CCl_4) 3420, 2960, 2860, 1662, 1622, and 1607 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.20 (s, 6 H), 1.27 (s, 3 H), 3.03 (s, 1 H), 6.00 (s, 1 H), 6.08 (d, J = 10 Hz, 1 H) and 6.73 ppm (d, J = 10 Hz, 1 H).

Irradiation of 1b in glacial acetic acid. A solution of 1.00 g (.00495 mole) of 1b in 250 ml of freshly distilled glacial acetic acid was irradiated for 0.75 h. The excess solvent was removed at reduced pressure and the resulting yellow oil taken up in ether-water. Extraction of the ether with saturated aqueous sodium bicarbonate, followed by drying and removal of solvent yielded 1.31 g (101%) of a yellow oil. This material was carefully chromatographed on florisil, with each fraction being monitored by TLC. The only identifiable material that was isolated was eluted with 25% ether in hexane. This fraction yielded 0.920 g (71%) of 5b: mp 64-66° (from hexane); ir (CCl_4) 2990, 2920, 2870, 1737, 1718 and 1610 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.05 (s, 3 H), 1.12 (s, 3 H), 1.17 (s, 3 H), 1.93 (s, 3 H), 3.73 (t, J = 3 Hz, 1 H) and 5.97 ppm (t, J = 1.6 Hz, 1 H); uv λ_{max} (95% EtOH) 241 nm (ε 11,800).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.39; H, 8.43.

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1. This investigation was supported by Public Health Service Research Grants No. GM 15044 from the National Institute of General Medicine and No. CA 12193 from the National Cancer Institute.

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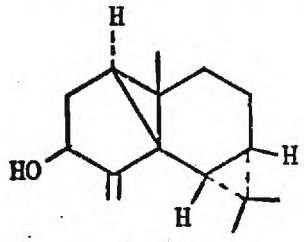

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16. Examination of models of 14 indicates that it is more sterically crowded than 13 because of the β-methyl group on the dimethylcyclopropane ring. Steric crowding is particularly severe in 14a where a methyl substituent is present at C-4.

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The Photochemical Conversion of Methoxy-Substituted 6/6-Fused Cross-Conjugated Cyclohexadienones into Isomeric Tricyclodecenones[1]

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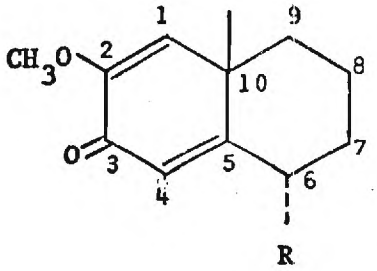
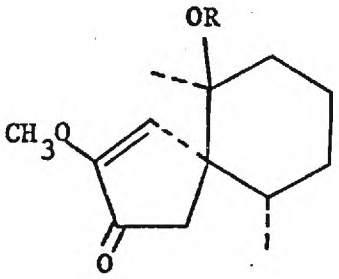
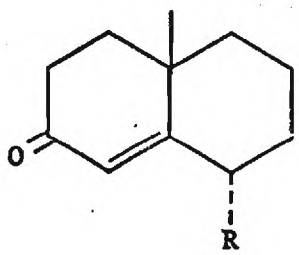
Abstract

2-Methoxy 6/6-fused cross-conjugated cyclohexadienones of the type 1 were irradiated in anhydrous dioxane. In addition to the expected lumiproducts, novel isomeric tricyclodecenone derivatives of the type 5 were obtained as primary photoproducts. Phenolic compounds tentatively assigned structures of the type 6 were also produced as primary photoproducts. The structure of the p-iodobenzoate 14, a heavy-atom derivative of the tricyclodecenone 5b, was established by x-ray crystallography. Possible modes of formation of enones of the type 5 are discussed.

Recently, we reported the synthesis of the 2-methoxy 6/6-fused cross-conjugated cyclohexadienone 1a and investigated its photochemical behavior on irradiation in protic solvents such as glacial and aqueous acetic acid.[2] The expected spiro acetoxy and spiro hydroxy enones 2a and 2b, respectively, were obtained and shown to be useful intermediates for the total synthesis of (±)-α-vetispirene.[2] We have now carried out irradiations of 1a and the related normethyl dienone 1b in the aprotic solvent dioxane and wish to report these results.





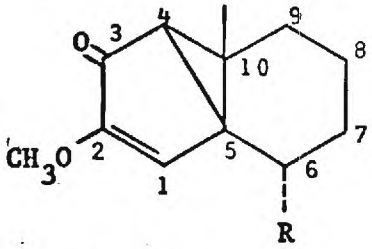


1a R=CH_3 2a R=Ac 3a R=CH_3

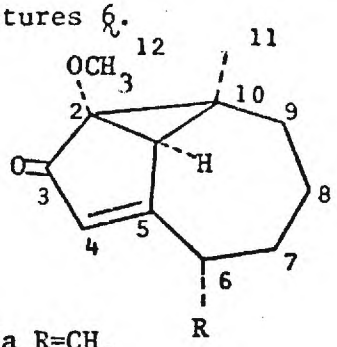
b R=H b R=H b R=H

Dienone 1b was prepared from the octalone 3b by a route similar to that employed for the synthesis of 1a from the corresponding octalone 3a.[2] Dilute solutions (ca 0.5%) of 1a or 1b in anhydrous dioxane were irradiated for 6.0 h at room temperature with a 7-watt Hanau NK-20 low pressure mercury lamp. Analysis of the photolysis mixtures by gas-liquid chromatography (GLC) using an internal standard showed that two tricyclic enones and a phenol were produced in ca 25%, 15%, and 15% yields each from each of the dienones. In each case ca 15% of the starting dienone remained at the end of the irradiation period. On the basis of the evidence presented below the major enones were

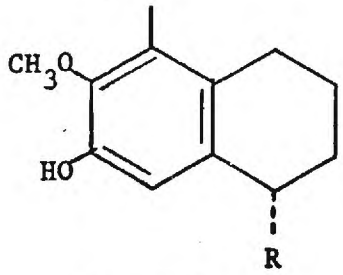
assigned the normal lumiproduct structures 4 while the minor enones were assigned the tricyclic structures 5. The phenolic products have been tentatively assigned the structures 6.



4a R=CH_3
b R=H



5a R=CH_3
b R=H

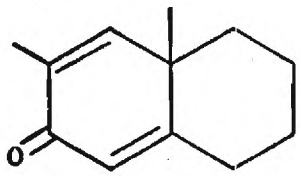


6a R=CH_3
b R=H

The phenolic products appeared to be primary photoproducts based on experiments in which a mixture of the isolated enones 4b and 5b were irradiated under similar conditions to the dienones 1. In neither case were detectable amounts of the phenol 6b formed. Enone 5b was essentially unchanged under the irradiation conditions, whereas 4b was almost completely destroyed, being largely converted into non-volatile material. In one run the course of the photolysis of dienone 1b was monitered carefully by GLC analysis. This revealed that after a short irradiation period, before 4b was further rearranged, the kinetic ratio of primary photoproducts 4b and 5b was 4.4:1.

The tentative assignments of the structures of the phenols 6 was by analogy to the work of Kropp[3] in which the 2-methyl dienone 7 was shown to yield the phenol 8 as a primary photoproduct on irradiation in methanol or acetic acid. Phenol 8 was produced by a photochemically induced 1,2-methyl shift. This was a novel rearrangement pathway since cross-conjugated do not generally yield phenols as primary photoproducts. Phenolic products are often observed in dienone photolysis, but they normally arise by secondary processes in which initially formed lumiproducts are further rearranged.[4]

Since phenols are formed as primary products from the irradiation of the 2-methoxy dienones it seems likely that they are also derived from a simple 1,2-methyl shift.



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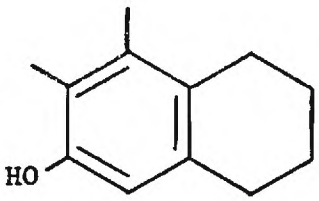

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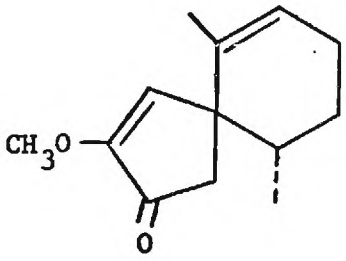
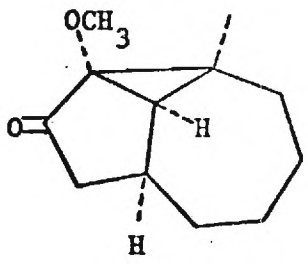


9

The spectra properties of the lumiproducts 4a and 4b were consistent with the assigned structures (see Experimental Section). In addition, compound 4a was converted into the known spiro dienone 9[2] by cleavage of the external bond of the cyclopropane ring with sulfuric acid in acetic anhydride under the conditions described by Marshall and Johnson[5] for the conversion of the related normethoxy lumiproduct into the corresponding spiro dienone. This information seemed to provide excellent evidence for the structural assignments.

The spectral properties of the enones 5a and 5b as well as those of the dihydro derivative 10 of 5b were also consistent with the assigned structures (See Experimental Section), but they did not permit positive assignment of the relative stereochemistry at C-1 and C-10. Clearly, if the stereochemical assignment at C-10 were reversed a much more highly strained system would result. However, strained systems such as the tricyclodecene derivative 11 which has trans-fused three and seven-membered rings

have been produced in photochemical reactions.[6] This raised the possibility that isomers of 5a and 5b with the 10-methyl groups β could have been produced in the irradiations of the corresponding dienones.



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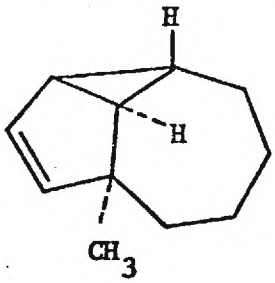

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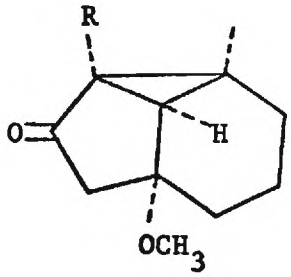
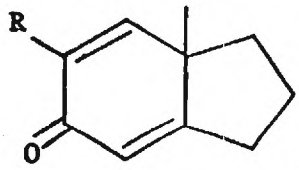
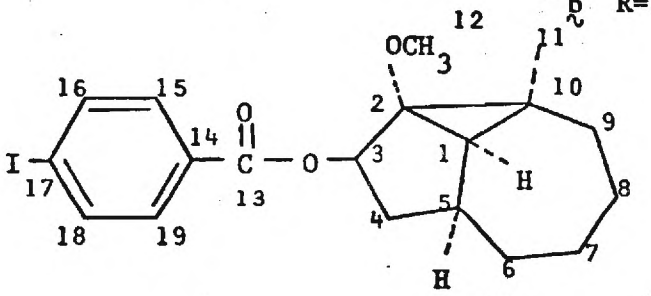


12a R=H
b R=CH$_3$



13a R=H
b R=CH$_3$



14

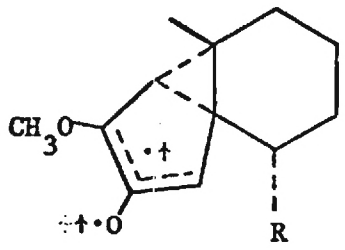
Irradiations of unsubstituted and methyl substituted 6/6-fused dienones of the type 1 and related compounds in dioxane normally yields lumiproducts of the type 4 and derived secondary photolysis products[4,7], but no isomeric primary photoproducts related to 5 have been observed in these systems.[8] Likewise, irradiations of α-halosantonin derivatives in nonprotic media has been reported to yield only lumisantonin derivatives related to 4.[9] However, the tricyclononanones such as 12 which we obtained upon irradiation of 6/5-fused dienones of the type 13 in methanolic acetic acid were considered to arise via 1,4-addition of methanol to strained tricyclononenones related to 5.[10]

Since the stereochemistry of compounds of the type 5 was of crucial importance with regard to their mechanism of formation, a derivative of 5b was prepared for use in a single-crystal x-ray crystallographic analysis. Catalytic hydrogenation of 5b gave the tricyclodecanone 10. Reduction of the carbonyl group in 10 with lithium tri(t-butoxy)aluminum hydride in tetrahydrofuran (THF) and reaction of the alcohol with p-iodobenzoyl chloride in pyridine gave the crystalline p-iodobenzoate derivative 14. The details of the determination of the structure of 14 by x-ray analysis are given in the Experimental Section. The molecular structure of 14 (with the p-iodobenzoate group deleted) is shown in Figure 1. This provided unambiguous proof of the structural assignment of 5b and the structure of 5a followed by analogy.

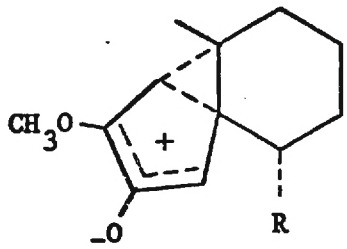
[Fig. 1]

The abnormal enones 5a and 5b may be considered to arise by a symmetry-allowed 1,4-sigmatropic rearrangement in a cyclopropyl intermediate of the type 15 produced by electronic excitation and β,β-bonding in the dienone system[4,11a-d] or by a photo-induced [σ2a + π2a] cycloaddition process involving the 5,10 σ and the 1,2 π bond of the dienone.[9b] The former process would occur with relention of configuration at C-10 while the latter would involve inversion at C-10.[11b] In the two methoxy dienones studied, the abnormal rearrangement pathway competes only to a minor, although significant, extent with the normal mode of rearrangement involving either election demotion in 15 to produce the ground state dipolar species 16 followed by a 1,4-sigmatropic shift or a photo-induced [σ2a + π2a] cycloaddition involving the 1,10 σ and the 3,4 π bonds of the dienone.[10]

The exact manner in which the methoxyl group influences these rearrangements is not clear. Its presence may increase the lifetime of triplet species such as 15 to allow time for rearrangement prior to election demotion or it may cause selective excitation of the 3,4 π bond of the dienone. It is known that α-methoxy substituents and other polar groups may influence the energy of the lowest lying excited states of α,β-unsaturated ketones.[12]



15a R=CH_3
b R=H



16a R=CH_3
b R=H

Experimental Section[13]

Preparation of 2-methoxy-3-keto-10-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1b). To a solution of 41.0 g (0.093 m) of lead tetraacetate in 200 mL of glacial acetic acid and 20 mL of acetic anhydride was added 10.0 g (0.061 m) of 3-keto-10-methyl-$\Delta^{4,5}$-octahydronaphthalene (3b).[14] The reaction mixture was stirred under nitrogen at 70-80° for 24 h. The bulk of the solvent was removed under reduced pressure and the residue was partitioned between ether and water. The ether layer was extracted with saturated sodium bicarbonate, dried, and the solvent removed in vacuo. Distillation of the residue yielded 5.22 g (39%) of a mixture of 2α- and 2β-acetoxy-3-keto-10-methyl-$\Delta^{4,5}$-octahydronaphthalene: bp 100-130° @ 0.005 mm; ir ($CHCl_3$) 1740, 1686 and 1619 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.25 (s, 0.6 H), 1.38 (s, 0.4 H), 2.07 (s, 3 H), 5.23 (broad t, 1 H), 5.62 (broad s, 0.4 H) and 5.67 ppm (broad s, 0.6 H).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.09; H, 8.16.

The mixture of acetoxy enones (2.26 g, 0.0102 m) was dissolved in 150 mL of methanol and a solution of 1.2 g (0.022 m) of potassium hydroxide in 10 mL of water was added. While a slow stream of oxygen was being passed through the solution, it was stirred for 24 h at room temperature. The excess methanol was removed in vacuo and the residue partitioned between ether and water. The aqueous layer was extracted with two 50-mL portions of ether and the ether extracts were discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted thoroughly with ether. The combined ether extracts were dried and the solvent removed in vacuo. The viscous yellow residue was dissolved in 100 mL of dry t-butyl alcohol, stirred under nitrogen, and a solution of potassium t-butoxide (prepared from 0.45 g (0.115 g-at) potassium) in 50 mL of dry t-butyl

alcohol was added rapidly. After stirring for 0.5 h, 4.0 g (0.028 m) of methyl iodide was added in one portion and the reaction mixture was then heated under reflux. After ca 20 min the excess t-butyl alcohol was removed by distillation and 50 mL of water added. Extraction with ether, drying, and removal of the solvent in vacuo gave 0.98 g (50%) of a yellow oil which crytallized on standing. Recrytallization from ether yielded pure 1b: mp 106.5-107.0°; uv λmax (95% EtOH) 250 nm (ε 10,000); ir ($CHCl_3$) 1658, 1635 and 1615 cm^{-1}; nmr δ_{TMS}(CCl_4) 1.25 (s, 3 H, C10-CH_3), 3.58 (s, 3 H, C2-OCH_3), 5.58 (s, 1 H, C4-H), and 5.93 ppm (broad s, 1 H, C1-H);

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.75; H, 8.23.

Irradiation of 1a. A solution of 1.00 g 6α-methyl-2-methoxy dienone 1a[2] in 150 mL of dry dioxane and irradiated for 6.0 h. The solvent was removed in vacuo and the residue subjected to GLC analysis (Column A)[13] using acetophenone as an internal standard. Response factors were calculated from GLC analysis of mixtures of the pure components (isolated by preparative GLC (Column B)[13]) and acetophenone. In one run, the results of this analysis were: compound 4a, 28%; compound 5a, 14%; phenolic compound 6a ca 15%; starting compound 1a, 14%.

The residue from three separate irradiations using a total of 2.8 g of dienone were combined and chromatographed on acetone-washed silica gel (60-200 mesh). Elution with 5% ether in hexane yielded an acidic compound tentatively assigned structure 6a (0.07 g, 6%) which showed: ir (CCl_4) 3550, 3410, 2925, 2860 and 1600 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.23 (d, J = 6 Hz, 3 H, C6-CH_3), 2.08 (s, 3 H, C1-CH_3), 3.68 (s, 3 H, C2-OCH_3), 5.48 (broad s, 1 H, C3-OH) and 6.57 (s, 1 H, C4-H). Further elution with 10% ether in

hexane yielded 1.16 g (41%) of a mixture of enones 4a and 5a (fraction A). Continued elution with 15% ether in hexane yielded a crystalline solid which had identical spectral properties to starting dienone 1a.

Fraction A was readily separated into two components by preparative GLC (Column B)[13]. The first material eluted from the column was 5a which showed the following properties: uv λmax (95% EtOH) 240 nm (ε 5,900); ir ($CHCl_3$) 2930, 1682 and 1585 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.18 (d, J = 6 Hz, 3 H, C6-CH_3), 1.27 (s, 3 H, C10-CH_3), 2.33 (s, 1 H, C1-H), 3.47 (s, 3 H, C2-OCH_3) and 5.47 ppm (s, 1 H, C4-H).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.41; H 8.94.

The longer retention time component was assigned structure 4a: uv λmax (95% EtOH) 234 (ε 7,800) and 285 nm (ε 2,200) (shoulder); ir ($CHCl_3$) 2940, 1695, and 1618 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.15 (s, 3 H, C10-CH_3), 1.22 (d, J = 6 Hz, 3 H, C6-CH_3), 1.67 (s, 1 H, C4-H), 3.65 (s, 3 H, C2-OCH_3) and 6.15 (s, 1 H, C1-H).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.41; H, 9.01.

Acid-catalyzed rearrangement of 4a. To a solution of 220 mg (2.07 mm) of lumiproduct 4a in 3.7 mL of acetic acid and 0.073 mL of acetic anhydride was slowly added 0.073 mL of concentrated sulfuric acid. The reaction mixture was stirred for 24 h, and then poured into cold 10% sodium hydroxide. Ether was added, and the ether layer was separated, washed with saturated aqueous sodium chloride, dried and the solvent evaporated in vacuo. This yielded 173 mg (79%) of a yellow oil which by GLC was mostly 9. Preparative GLC (column B)[13] gave a pure sample of 9 which showed essentially identical spectral properties to those previously reported.[2]

Irradiation of 1b. A solution of 1.00 g of 2-methoxy dienone 1b in 250 ml of dry dioxane was photolyzed for 6.0 h. The solvent was removed in vacuo and the residue subjected to GLC (Column A)[13] analysis using acetophenone as an internal standard. In one run, the results of this analysis were; compound 4b, 31%; compound 5b, 18%; compound 6b, 12%; compound 1b, ca 15%. In another run the photolysis mixture was analyzed after 15 min and showed that the ratio of 5b to 4b was 4.4 to 1.0 with about 96% of dienone 1b remaining.

The products of five, separate photolysis runs were combined and chromatographed on silica gel. Elution with 15% ether in hexane gave a product (496 mg, 9.9%) tentatively identified as the phenol 6b: ir (CCl_4) 3550, 3420, 2930, 2860 and 1597 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.70 (m, 4 H, C7-H, C8-H), 2.05 (s, 3 H, C1-CH_3), 2.50 (m, 4 H, C6-H, C9-H), 3.65 (s, 3 H, C2-OCH_3), 5.50 (broad s, 1 H, C3-OH) and 6.42 ppm (s, 1 H, C4-H). Further elution with 25% ether in hexane gave a 1.65 g (33%) mixture of 4b and 5b (Fraction A). Continued elution with pure ether yielded a crystalline solid that had identical spectral properties to starting dienone 1b.

Fraction A was separated into two components by careful column chromatography on silica gel. Elution with 30% ether in hexane yielded 405 mg (8.1%) of pure 4b: uv λmax (95% EtOH) 237 (ε 8,000) and 285 nm (ε 2,200) (sholder); ir ($CHCl_3$) 2935, 1700, 1620 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.17 (s, 3 H, C10-CH_3), 1.61 (s, 1 H, C4-H), 3.60 (s, 3 H, C10-OCH_3) and 5.90 ppm (s, 1 H, C1-H); m/e (70 ev) 192.117 (EMC = 192.115). Further elution with 40% ether in hexane yielded 425 mg (8.5%) of pure 5b: uv λmax (95% EtOH) 241 nm (ε 5,400); ir ($CHCl_3$) 2930, 1682, 1590 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.26 (s, 3 H, C10-CH_3), 2.32

(s, 1 H, C1-H), 3.48 (s, 3 H, C2-OCH_3) and 5.50 ppm (s, 1 H, C4-H); m/e (70 ev) 192.113 (EMC = 192.115).

Anal. Calcd. for $C_{12}H_{16}O_2$; C, 74.96; H, 8.39. Found: C, 74.72; H, 8.45.

Irradiation of 4b and 5b. A mixture of 45 mg of 4b and 5 mg of 5b was dissolved in 100 ml of dry dioxane and photolyzed for 0.5 h. The solvent was removed in vacuo and the residue analyzed by GLC. This analysis showed that 4b had completely disappeared whereas the amount of 5b remained essentially unchanged. Only trace amounts of other volatile components were produced. No volatile photoproduct with a retention time corresponding to phenol 6b was obtained.

Hydrogenation of 5b. A solution of 425 mg of 5b in 100 mL of 95% ethanol was mixed with 400 mg of 10% palladium-on-carbon in a pressure bottle, and shaken on a Parr apparatus at 40 psi hydrogen pressure for 4.0 h. The catalyst was removed by filtration and the solvent removed in vacuo. This yielded 362 mg (85%) of 10 (pure by GLC analysis) which showed: mp 52-53° (from pentane); ir ($CHCl_3$) 2930 and 1718 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.18 (s, 3 H, C10-CH_3), 1.73 (d, J = 6 Hz, 1 H, C1-H), three peaks at 2.00, 2.03 and 2.17 (J = 8.8 and 10.0 Hz, 2 H, C4-CH_2, gemial coupling not observable), 2.67 (m, 1 H, C5-H) and 3.34 ppm (s, 3 H, C2-OCH_3); m/e (70 ev) 194.131 (EMC = 194.131).

Preparation of the p-Iodobenzoate 14. To a mixture of 107 mg (2.81 mm) of lithium aluminium hydride and 50 mL of dry tetrahydrofuran (THF) was added 0.79 mL (625 mg, 8.43 mm) of dry t-butyl alcohol with stirring under nitrogen. A solution of 362 mg (1.87 mm) of 10 in 4 mL of dry THF was added dropwise with stirring over a 10-min period and stirring was continued at

room temperature for 1.0 h. The reaction mixture was poured into excess hydrochloric acid and extracted with three 50-mL portions of ether. The combined ether extracts were back extracted with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride and then dried and the solvent was removed in vacuo. This gave 370 mg (101%) of material which did not have significant infrared absorption at 1718 cm^{-1}. This material (370 mg, 1.89 mm) was dissolved in 5 mL of dry pyridine and 755 mg (2.83 mm) p-iodobenzoyl chloride (Eastman 9541, mp 63-65°) was added with stirring over a 10-min period. This mixture was allowed to stand for 48 h at room temperature and then poured into a mixture of 50 g of ice and 10 mL of concentrated hydrochloric acid. After stirring for ca 5 min the mixture was extracted with three 50-ml portions of ether. The ether extracts were washed with water, dried, and the solvent removed in vacuo. This yielded a yellow oil that was chromatographed on silica gel. Elution with 20% ether in hexane gave 415 mg (52%) of crystalline iodobenzoate 14 which showed: mp 110-111° (from hexane); nmr δ_{TMS} (CCl_4) 1.17 (s, 3 H, C10-CH_3), 3.28 (s, 3 H, C2-OCH_3), 5.90 (t, J = 8 Hz, 1 H, C3-H) and 7.67 ppm (s, 4 H, aromatic-H).

Anal. Calcd. for $C_{19}H_{23}O_3I$: C, 53.53; H, 5.44. Found: C, 53.43; H, 5.47.

A single crystal suitable for X-ray analysis was prepared by dissolving 50 mg of 14 in 1.0 mL of hexane and five drops of toluene. The solid was brought into solution by heating to about 55°, and the solution was then allowed to cool overnight in a Dewar flask that contained water heated to 55°.

Crystallographic Data Collection. A needle-shaped crystal with approximate dimensions 0.2 x 0.2 x 0.4 mm. was mounted on a glass fiber using epoxy cement such that the longest crystal dimension was approximately parallel to the fiber axis.

Unit cell parameters and the orientation matrix were determined on a Syntex $P2_1$ four circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle = 12.2°) using MoK_α radiation at a takeoff angle of 6.5°. Fifteen reflections whose 2θ values ranged from 6.0° to 24.0° were machine-centered and used in least-squares refinement of the lattice parameters and orientation matrix. Unit cell parameters obtained were a = 7.073 (2) Å[15], b = 23.354 (14) Å, c = 11.049 (7) Å, α = 90.0, β = 91.05 (4)°, γ = 90.0, and V = 1824 (2)Å^3. The calculated density of 1.55 g cm^{-3} for four formula units per unit cell agrees with the experimental density of 1.48 g cm^{-3} measured by the flotation method using aqueous zinc chloride. Omega scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.25°, indicating a satisfactory mosaic spread for the crystal.

Axial photographs indicated that the crystal belonged to the monoclinic system. Intensity data for zero and upper levels were collected at a rapid scan rate and the intensities examined carefully for systematic absences. The absence of h01 with h+1 = 2n+1 and 0k0 with k = 2n + 1 reflections is consistent with only space group $P2_1/n$.

Intensity data were collected using θ-2θ scans with x-ray source and monochromator settings identical to those used for determination of the unit cell parameters. A variable scan rate of from 4.5 to 29.3°/min was used and a scan width of 2° was sufficient to collect all of the peak intensity.

Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time ratio, TR, of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (0,0,10; 0,8,0; 2,0,0) monitored every 100 reflections. Intensities were calculated from the total scan count (CT) and background counts by the relationship:

$$I = CT-(TR)(bdg1 + bgd2).$$

The intensities were assigned standard deviations according to the formula

$$\sigma(I) = [CT + (TR)^2(bgd1 + bgd2) + (pI)^2]^{1/2}$$

from a total of 5223 reflections collected in a complete quadrant of data out to $2\theta = 60°$; 2454 were accepted as statistically above background on the basis that I was greater than $3\sigma(I)$. Lorentz and polarization corrections were made in the usual way.

Solution and Refinement of the Structure. Computations were performed using standard programs;[16] all computations were carried out on the CDC Cyber 74 system. For structure factor calculations the scattering factors were taken from Cromer and Waber's tabulation[17] for all atoms. The scattering factor for iodine was corrected for the real and imaginary anomalous dispersion components, using the dispersion factors given by Cromer.[18] The agreement factors are defined in the usual way as

$$R = (\Sigma||F_o|-|F_c||)/(\Sigma|F_o|)$$

and

$$R_w = [\Sigma w(|F_o|-|F_c|)^2/\Sigma w(|F_o|)^2]^{1/2}$$

In all least squares refinements, the quantity minimized was $w(|F_o|-|F_c|)^2$. A wighting scheme based on counting statistics ($w = 4I/\sigma^2(I)^2$) was employed for calculating R_w and in least-squares refinement.

Coordinates for the iodine atom were obtained from a three-dimensional Patterson synthesis; successive cycles of least-squares refinement and electron density calculation revealed the position of all carbon and oxygen atoms; hydrogen atoms were not located. All atoms were refined anisotropically. Least-squares refinement converged to give the residuals $R = 0.056$ and $R_w = 0.050$ (2454 observations, 208 variables). In the final refinement no parameter changed by more than one standard deviation from the previous value.

Supplementary Material Available. Tables 1 and 2 listing final positional parameters and calculated and observed structure factors, respectively, are available. Ordering information is given on any current masthead page.

References and Notes[13]

1. This investigation was supported by Grant Number CA 12193, awarded by the National Cancer Institute, DHEW.

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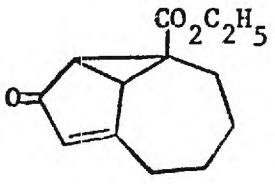
8. Professor P. J. Kropp has informed us that the tricyclodecenone i is produced as a minor product of irradiation of the angular carboethoxydienone ii in dioxane. However, the stereochemistry of this photoproduct was not established.



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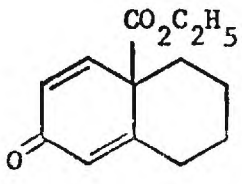

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12. a. R. L. Cargill, W. A. Bundy, D. M. Pond, A. B. Sears, J. Saltral, and J. Winterle, Mol. Photochem., 3, 123 (1971); b. G. Marsh, D. R. Kearns, and K. Schaffner, Helv. Chem. Acta., 51, 1890 (1968).

13. Melting and boiling points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 457 infrared spectrophotometer. Ultraviolet spectra were measured using a Beckman Model 25 recording spectrophotometer using 1 cm matched quartz cells. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethyl silane. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-7 or a Varian M-66 spectrometer. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, Ga. Gas-liquid chromatography was carried out using a Perkin-Elmer 881 or an Areograph A-90-P3 gas chromatograph. The following columns were used: A (6 ft. x 0.125 in., 20% Carbowax K-20M on Chromsorb W); B (10 ft. x 0.25 in., 20% Carbowax K-20 M on Chromosorb W).

Irradiations were conducted using a seven-watt Hanau NK 20 low pressure mercury lamp. Solutions were agitated with a stream of nitrogen for a few minutes preceeding and during the irradiation period. Anhydrous magnesium sulfate was employed as the drying agent. Dioxane was distilled from sodium metal prior to use.

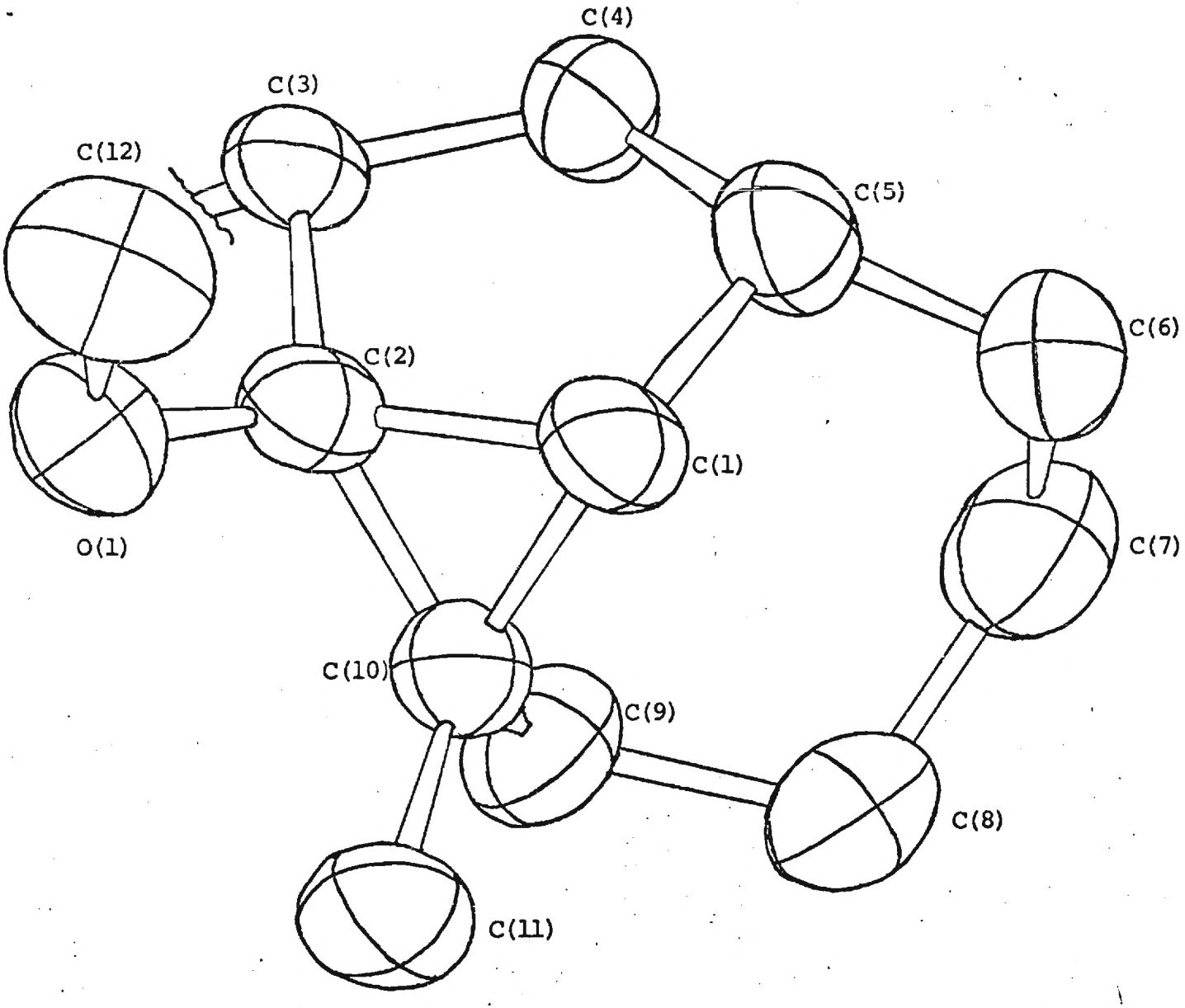
14. N. C. Ross and R. Levine, J. Org. Chem., 29, 2341 (1964).

15. Numbers in parentheses here and elsewhere in this paper indicate estimated standard deviations in the least significant digit(s).

16. Programs utilized were Zalkin's OFRDAP Fourier summation program, Iber's NUCLS modification of the Busing-Martin-Levy least-squares program, Doeden's RBANG rigid group orientation program, Stewart's ABSORB absorption correction program from the X-Ray 72 system, and Johnson's ORTEP program.

17. D. T. Cromer and J. T. Waber, Acta Crystallogr, 18, 104 (1965).

18. D. T. Cromer, Acta Crystallogr., 18, 17 (1965).



Figure

G-33-612

August 22, 1977

FINAL PROGRESS REPORT

Photochemical Synthesis of Sesquiterpenes
CA 12193
Drury S. Caine III, Principal Investigator
School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

Results Which Have Been Published (Reprints not previously submitted are attached).

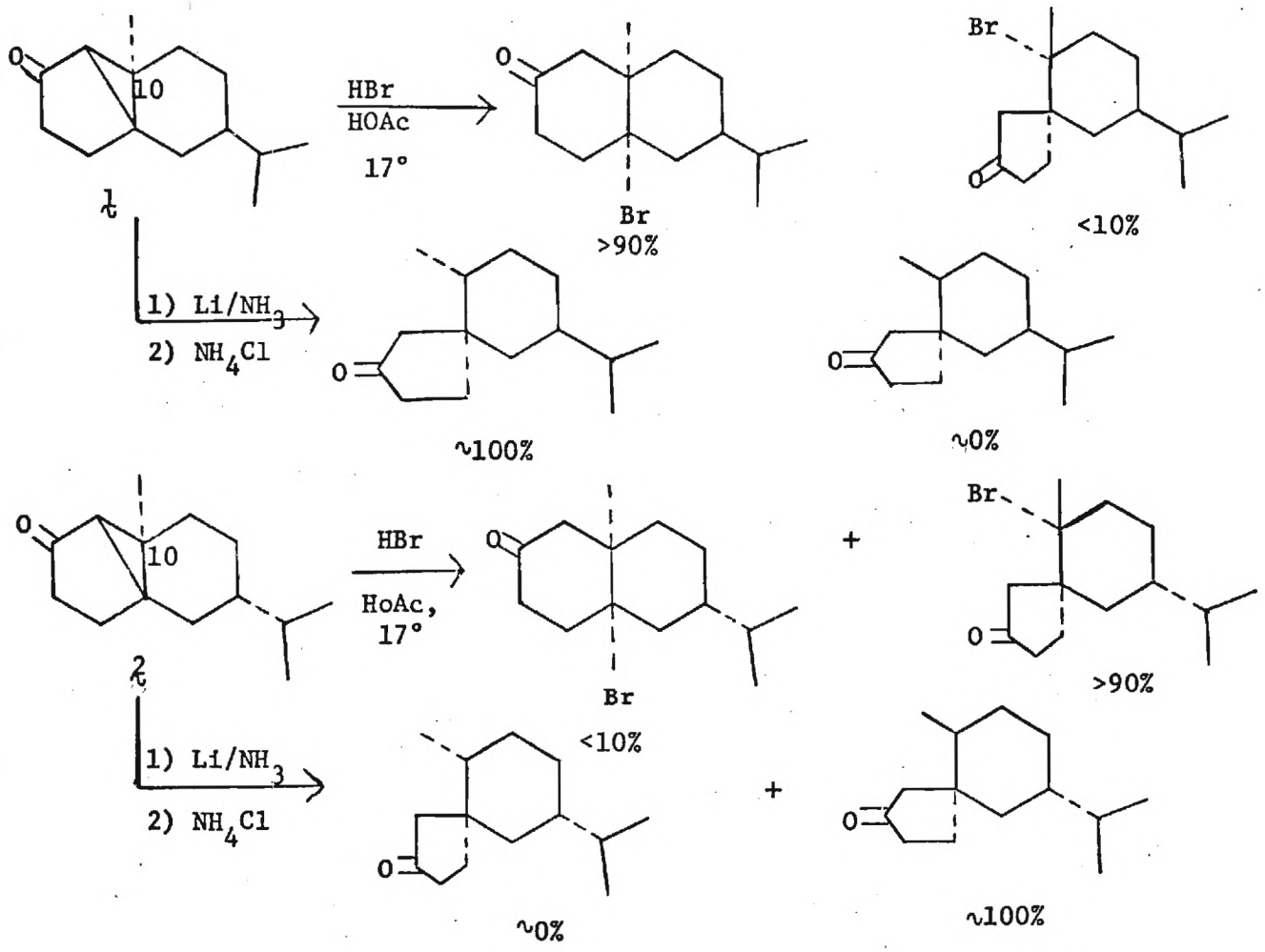
The following sesquiterpenes were totally synthesized in connection with the work: (±)-Oplopanone, (-)-Cyclocolorenone, (+)-α-Cyperone, (±)-Yomogin, (-)-4-Epiglobulol, (+)-4-Epiaromadendrene, and (±)-α-Vetispirene. Relay syntheses of the following sesquiterpenes were accomplished: β-Vetivone, 10-Epi-β-vetivone, and Anhydro-β-rotunol. The influence of electron withdrawing substituents on the dienone chromophore on the course of photochemical rearrangements of 6/6-fused cross-conjugated dienones was explored and the photochemical behavior of unsubstituted and methyl-substituted 6/5-fused dienones in protic and aprotic solvents was studied. In the latter case a novel type of photoproduct was isolated. A short, convenient synthesis of 6c,10-dimethyl(r-5-C')spiro[4.5]dec-6-en-2-one, a precursor to the spirovetivanes sesquitepenes was developed. It was found that nootkatane and spirovetivane carbon skeletons could be interconverted by photolysis of cross-conjugated cyclohexadienone intermediates. A tricyclic cyclopropyl ketone having a carbon skeleton related to 10-epieudesmane was found to undergo rearrangement to 11,12-dihydronootkatone upon treatment with boron trifluoride in methylene chloride.

Results For Which Papers Have Been Accepted or Submitted For Publication
(Copies of preprints are attacked)

(±)-α-Cadinol and (±)-3-oxo-α-cadinol have been totally synthesized using the photochemical rearrangement of an appropriate 6/5-fused cyclohexadienone in glacial acid to produce a 5/6-fused acetoxy enone followed by expansion of the A ring to a six-membered ring. Tricyclic cyclohexadienones related to epimaalienone were found to yield tetracyclic cyclopropyl ketones having the ring system of the tetracyclic sesquiterpene myliol on irradiation in dioxane. The same compounds gave tricyclic enones having a 5/7-fused A/B-ring system on irradiation in glacial or aqueous acetic acid. Metal-ammonia reduction of cis-8,10-diemthyl-1(9)-octal-2-one was found to yield considerably more of the cis-decalone reduction product than the corresponding transdimethyl octalone when treated with lithium in liquid ammonia. Also, the ratio of the cis to the trans decalone was found to be dependent upon the nature of the metal. Ultraviolet irradiation of 2-methoxy-6/6-fused cross-conjugated cyclohexadienones was found to yield the expected lumiproducts and also novel isomeric tricyclodecenones and phenols as primary photoproducts. The structure of the novel tricyclodecenones was established by a single crystal x-ray analysis on a crystalline derivative from one series.

Essentially Complete Work Which Is Being Prepared For Publication

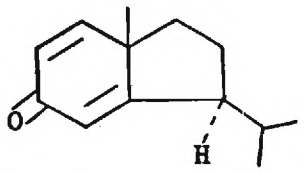
The tricyclodecanones $\underset{\sim}{1}$ and $\underset{\sim}{2}$ have been synthesized and cleavage of the cyclopropane ring in these compounds has been carried out with hydrogen bromide in acetic acid and lithium in liquid ammonia. The results of these reactions are indicated on the next page.



The results of the hydrogen bromide ring cleavages suggest that the reactions are kinetically controlled and that opening of the three-membered ring occurs in a diaxial fashion with respect to the more stable conformation of the six-membered ring. The results of the lithium ammonia cleavages which are highly stereoselective indicate that the tertiary carbanionic center at C-10 achieves the more stable configuration prior to protonation by liquid ammonia. As expected in both 1 and 2 the external bond of the cyclopropane ring which overlaps with the pi bond of the carbonyl group undergoes reductive cleavage.

Other Results

In connection with the proposed photochemical approach to the spiro sesquiterpenes acorenone and acorenone-B, the 6/5-fused dienone 3 was converted into the tricyclic ketone 4 by irradiation in dioxane followed by catalytic hydrogenation. The cyclopropane ring in 4 was cleaved with lithium in liquid ammonia to produce a ca. 1:1 mixture of the spirononanones 5 and 6. Ketone 5 which has a cis relationship of the methyl and isopropyl groups was needed for the synthesis of the natural products. However, 5 and 6 were difficult to separate by chromatographic methods. This coupled with the poor stereoselectivity in the ring opening reaction has caused us to abandon this approach.



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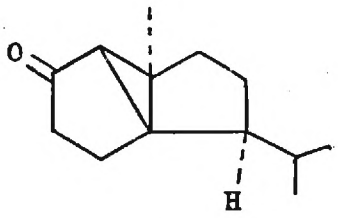

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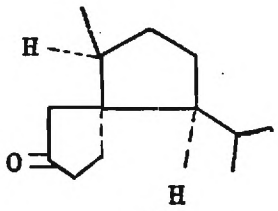

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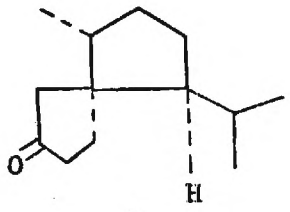

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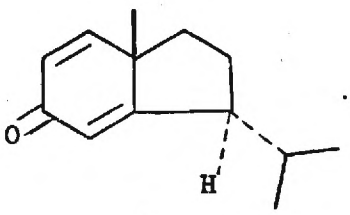

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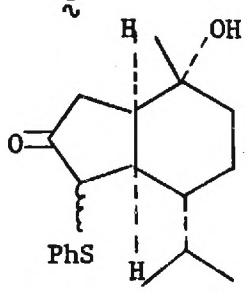

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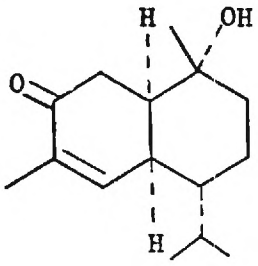

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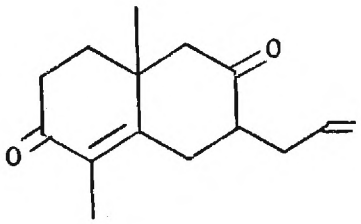

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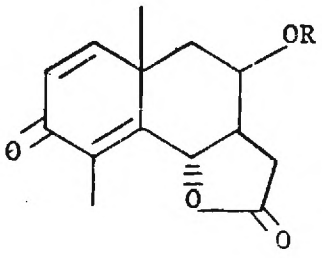
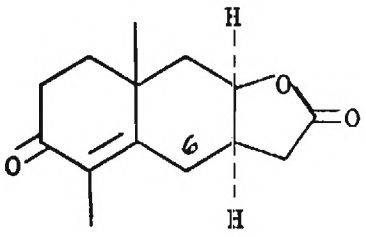


11

In connection with the proposed synthesis of T-muurolol, the dienone 7 has been obtained and converted into the 5/6-fused α-thiophenylhydroxy ketone 8. By addition of ethyllithium to the carbonyl group in 8 followed by cleavage of the α-thiophenyl alcohol with lead tetraacetate, hydrolysis, and cyclization 3-oxo-T-muurolol 9 should be obtained. We intend to complete the synthesis fo T-muurolol via 9.

In connection, with the proposed synthesis of euparotin the keto enone 10 has been prepared. This intermediate should be convertible into the dienone 11 which upon irradiation in aqueous acetic acid should yield a hydroazulene derivative having the ring system of euparotin.

Methods of allylic oxidation applicable to the conversion of the enone lactone 12 into its 6α-hydroxy derivative have been investigated. In a model study we hoped to prepare the α-thiophenyl ketone 13 and convert it to the 6α-hydroxy ketone 14 by oxidation to the sulfoxide followed by allylic rearrangement and O-S bond cleavage. However, efforts to prepare 13 by phenylsulfenylation of the conjugate enolate 15 of 1,10-diemthyl 1(9)-octalin-2-one led to variable results. Mixtures of 13 and the corresponding 6-sulfenylation product 16 were produced. The 13/16 ratio has been shown to be dependent upon the nature of the sulfenylating agent and the metal cation. We are continuing to explore sulfenylations of conjugate enolates to determine the factors which favor α vs γ attack. Efforts to convert 13 into 14 are also in progress.



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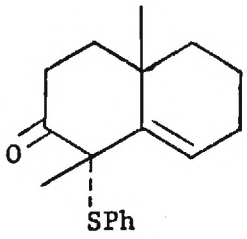

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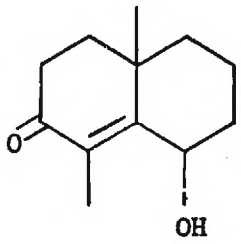

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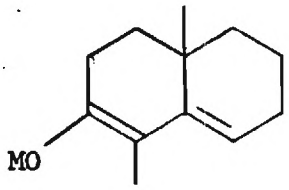

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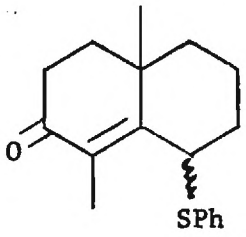
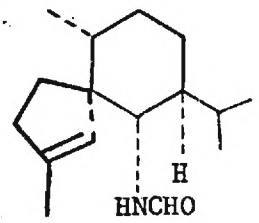


16

In connection with a photochemical approach to the synthesis of the novel spiro sesquiterpene axamide-3 (17) the tricyclic enone 18 has been synthesized. The conversion of 18 into 17 by approaches involving cleavage to the external bond of the cyclopropane ring are being explored.



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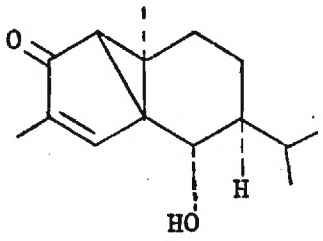

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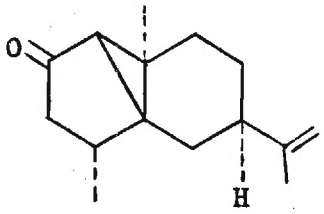

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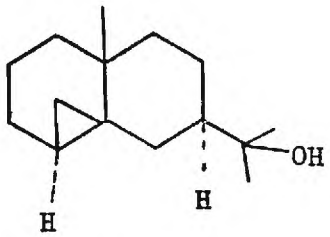
Treatment of the tricyclic enone 19 with the acetylmethanesulfonate in methylene chloride has been found to yield a mixture of products containing (+)-nootkatone. Further investigation of this ring opening followed by a biogenetic-like methyl migration is in progress. Other work includes the synthesis of the tricyclic alcohol 20 which is apparently a stereoisomer of cycloeudesmol.



20

List of Publications of Drury S. Caine III from Work Supported by CA 12193

"Photochemical Rearrangements of 6/5-Fused, Cross-Conjugated Cyclohexadienones. Application To The Total Synthesis of dl-Oplopanone." J. Am. Chem. Soc., 93, 6311 (1971), with F. N. Tuller.

"Photochemical Rearrangements of Bicyclic 6/5-Fused Cross-Conjugated Cyclohexadienones and Related Compounds," J. Org. Chem., 37, 706 (1972), with A. M. Alejandre, K. Ming, and W. J. Power, III.

"The Influence of Electron Withdrawing Substituents on the Photochemical Behavior of 6/6-Fused Cross-Conjugated Cyclohexadienones," J. Org. Chem., 38, 967 (1973), with J. F. DeBardeleben, Jr., P. F. Brake, and J. B. Dawson.

"The Photochemical Behavior of 6/5-Fused Cross-Conjugated Cyclohexadienones in Protic Solvents," Chem. Commun., 469 (1973), with J. T. Gupton, III, K. Ming, and W. J. Powers, III.

"The Total Synthesis of dl-Oplopanone," J. Org. Chem., 36, 3663 (1973), with F. N. Tuller.

"Interconversion of Nootkatane and Vetispirane Sesquiterpenes via Photolysis of Cross-Conjugated Cyclohexadienone Intermediates," Tetrahedron Letters, 703 (1974), with C. Y. Chu.

"A Convenient Stereospecific Synthesis of (+)-α-Cyperone," J. Org. Chem., 39, 2654 (1974), with J. T. Gupton, III.

"The Synthesis of dl,-Yomogin," Tetrahedron Letters, 743 (1975), with G. Hasenhuettl.

"Photochemical Rearrangements of Cross-Conjugated Cyclohexadienones. Application to the Synthesis of (-)-4-Epiglobutol and (+)-4-Epiaromadendrene," J. Org. Chem., 40, 809 (1975), with J. T. Gupton, III.

"The Stereospecific Synthesis of 6,c-10-Dimethyl-(r-5-C')-spiro[4.5]dec-6-en-2-one and its Conversion into (±)-α-Vetispirene." J. Org. Chem., 41, 1539 (1976), with A. A. Boucugnani, S. T. Chao, J. B. Dawson, and P. F. Ingwalson.

"A Convenient Photochmical Synthesis fo a Precursor to the Spirovetivanes," J. Org. Chem., 41, 3632 (1976) with A. A. Boucugnani and W. R. Pennington.

"The Acid-Catalyzed Rearrangement of a Cyclpropyl Ketone Related to 10-Epieudesmane," Tetrahedron Lett., 2521 (1976) with S. L. Graham.

"The Photochemical Total Synthesis of (±)-3-Oxo-α-cadinol and (±)-α-Cadinol," Tetrahedron Letters, in press, with A. S. Frobese.

"Photochemical Rearrangements of Cross-Conjugated Cyclohexadienones Related to Epimaalienone," J. Org. Chem., in press, with H. Deutsch and J. T. Gupton, III.

"Metal-Ammonia Reduction of Cis-8,10-Diemthyl-1(9)-octal-2-one," submitted for publication to J. Org. Chem., with T. L. Smith, Jr.

"The Photochemical Conversion of Methoxy-Substituted 6/6-Fused Cross-Conjugated Cyclohexadienones into Isomeric Tricyclodecenones," submitted for publication to J. Org. Chem., with H. Deutsch, S. T. Chao, D. G. Van Derveer, and J. A. Bertrand.

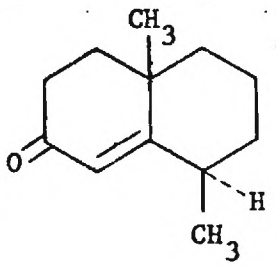
Metal-Ammonia Reduction of Cis-8,10-Dimethyl-1(9)-octal-2-one

Drury Caine and Troy L. Smith, Jr.

School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

Abstract

Lithium-ammonia reduction of the title enone 1 gave a 6.4:1 mixture of the corresponding trans- and cis-decalones 3 and 4, respectively. The trans-decalone 3 was also the major reduction product when sodium, potassium, calcium, and barium were employed as the metals for the reduction of 1. Within the alkali metal and alkaline-earth metal series the largest amounts of trans product were obtained with the smaller cations, i.e., Li^{+} and Ca^{+2}. An explanation for these results is offered. The ^{13}C NMR chemical shifts of the decalones 3 and 4 and of the isomeric decalones 6 and 7 prepared by lithium-ammonia reduction or catalytic hydrogenation of the enone 5 are also reported.



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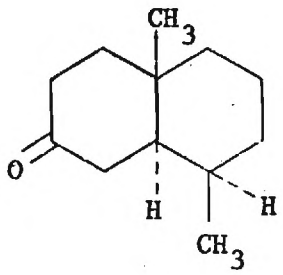

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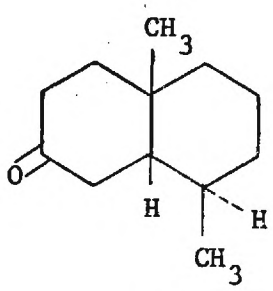

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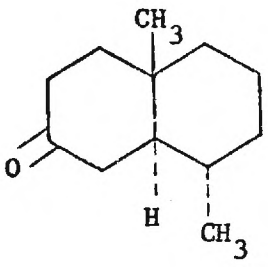

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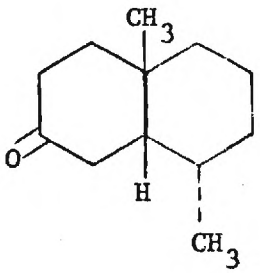

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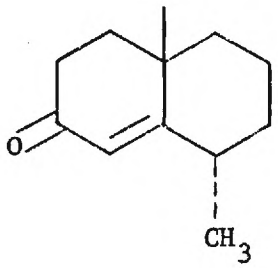


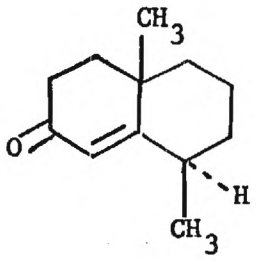
5

Metal-Ammonia Reduction of Cis-8,10-Dimethyl-1(9)-octal-2-one[1]

Drury Caine* and Troy L. Smith, Jr.

School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

Recently, we reported the synthesis of cis-8,10-dimethyl-1(9)-octal-2-one (1) by transfer hydrogenation of the bicyclic dienone 2.[2] The continued interest in the influence of substituents upon the stereochemistry of metal-ammonia reductions of 1(9)-octal-2-ones[3] has prompted us to investigate the stereochemistry of the reduction of 1 with lithium and other metals in liquid ammonia.



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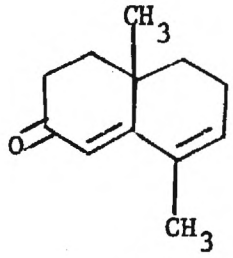
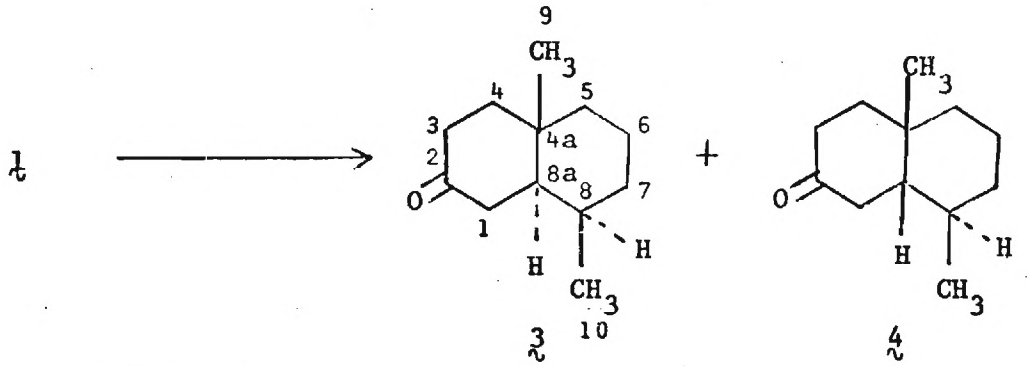


2

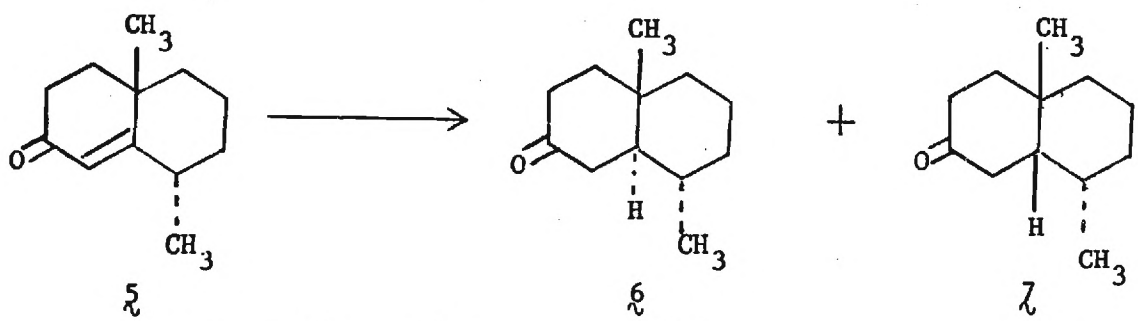
Reduction of 1 with lithium in liquid ammonia containing 1 equiv. of tert-butyl alcohol under the usual conditions gave a 6.4:1 mixture of the known trans-decalone 3[4] and an isomer which has been assigned the cis-decalone structure 4 in 85-91% yield. It was also found that catalytic hydrogenation of 1 using 10% palladium-on-carbon in 95% ethanol gave a 65:35 mixture of 3 and 4 in essentially quantitative yield.[5]

In order to acertain that isomerization of 1 into the thermodynamically more stable trans-octalone 5[6] was not occurring prior to chemical (or catalytic) reduction, the latter enone was converted to the corresponding decalone derivatives.



	3	4
Li/NH_3,ether	87%	13%
1 equiv t-BuOH		
H_2,Pd(C),95%EtOH	65%	35%

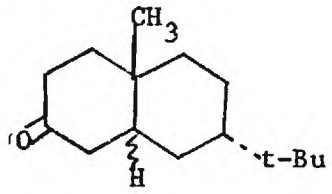
As expected lithium-ammonia reduction of 5 gave exclusively the trans-decalone 6[4b] and a 5:95 mixture of 6 and the cis isomer 7[7] was produced by catalytic hydrogenation of 5 in acidic 95% ethanol using 5% palladium-on-carbon as the catalyst. The isomeric decalones 3, 4, 6, and 7 were readily separated from each other by GLC using a Carbowax column. Thus no significant isomerization of 1 into 5 occurred under either set of reduction conditions.[5]



	6	7
Li/NH_3,ether	100%	—
1 equiv t-BuOH		
H_2,Pd(c),95%		
EtOH,HCl	5%	95%

The structural assignment of 4 is based upon the fact that it is formed along with 3 in both the chemical and catalytic reduction of 1 and upon a

comparison of its ^{13}C NMR spectrum with those of the other three isomeric decalones. The natural abundance ^{13}C chemical shifts of decalones 3, 4, 6, and 7 are recorded in Table I. These chemical shift assignments are consistent with off-resonance decoupling measurements. However, the assignments in parenthesis are tentative. A significant feature of these ^{13}C spectra is that the angular carbon atoms (C-9) in the two cis-fused isomers 4 and 7 occur at 6-10 ppm lower field than the corresponding absorptions in the trans isomers 3 and 6. The latter compounds have a greater number of γ interactions[8] which contribute to the shielding of the angular carbon atoms. The angular carbon atoms in the cis- and trans-fused decalones 8a and 8b have been reported to have chemical shifts of 27.0 and 17.2 ppm.[3b] This provides another example of a pair of 2-decalones in which the angular carbon of the cis isomer absorbs at lower field.



8a. cis ring fusion
b. trans ring fusion

Table I. Natural Abundance ^{13}C Chemical Shifts of trans- and cis-2-Decalones[a]

Decalone	Chemical Shifts of C Atoms[b]. 1	2	3	4	4a	5	6	7	8	8a	9	10
3	(43.8)	211.6	(40.6)	(43.7)	33.4	(38.2)	17.2	(32.8)	32.8	46.4	18.6	14.1
4	(39.6)	211.6	(37.6)	(39.6)	33.0	(35.9)	21.4	(31.4)	31.4	51.6	27.7	20.1
6	(41.2)	212.0	(40.9)	(40.9)	33.2	(37.8)	21.4	(35.6)	32.3	50.6	19.6	15.9
7	(41.1)	212.4	(36.9)	(37.5)	33.2	(28.7)	21.6	(27.7)	29.9	47.6	26.2	19.3

a. For the numbering system of the decalones, see structure 3. b. Chemical shifts are in ppm relative to internal TMS.

Systematic studies on the influence of the nature of the metal on the course of metal-ammonia reductions of α,β-unsaturated ketones are rare and have not been reported for 1(9)-decalones.[3c] Therefore, since enone 1 gave a mixture of isomers using lithium in liquid ammonia, we have determined the ratio of the reduction products obtained using other alkali and alkaline-earth metals under the same conditions. These results and the lithium-ammonia reduction results are recorded in Table II.

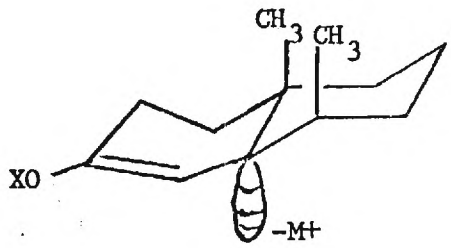
Table II. Reduction of Enone 1 with Metals in Liquid Ammonia Containing 1 Equiv of tert-Butyl Alcohol at -33°.

Metal	% 3[a]	% 4[a]	3:4 Ratio	% yield[b]
Li	86.5±2.3	13.6±2.3	6.4	85-91
Na	80.4±0.4	19.6±0.4	4.1	88-98
K	78.6±0.8	21.4±0.8	3.7	78-90
Ca	93.2±0.6	6.8±0.6	13.7	96-97
Ba	88.1±2.3	11.9±2.3	7.4	93-95

a. Percentages are an average of two or more runs. b. Range of isolated yields of decalone mixtures after GLC anlysis.

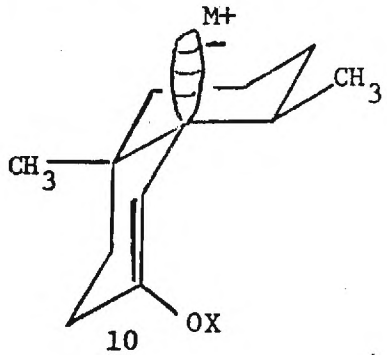
Decalones 3 and 4 may be considered to arise via protonation of β-carbanionic intermediates 9 or 10, respectively, in which the oxygen atom is either protonated[9] or associated with a metal cation.[3c] Intermediate 9 is favored over 10 on stereoelectronic grounds and as predicted by the Stork-Darling axial protonation rule[10] the trans-decalone 3 is the favored reduction product with all metals investigated. On the basis of estimates of non-bonded interactions alone, species 10 which leads to the cis product should be 2-3 kcal/mole more stable than 9. Therefore, the ratios of 3:4 observed under

various conditions support the previous suggestion that the orbital overlap (stereoelectronic) factor provides a stabilization energy of 3-5 kcal/mole.[3c]



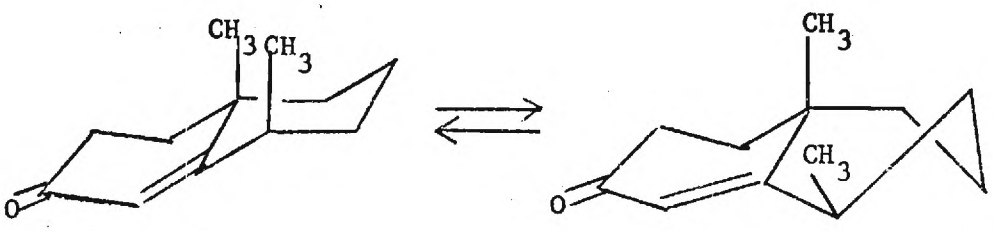
9

X=H- or M



10

The amount of cis product 4 obtained from 1 was small with lithium and the other metals studied but it was significantly greater than has been observed for other ring B substituted octalones except those having exceptionally bulky groups at the 6β or 7α positions.[3b,c] It seems to be generally true that when the B ring of the 1(9)-octal-2-one system is forced into an unusual conformation by substituent effects cis reduction products are observed.[3b] In the case of 1 conformation 1B in which the B ring is in a twist-boat and the 1,3-diaxial methyl-methyl interaction is relieved may be in equilibrium with conformation 1A in which the B ring is in a normal chair. On addition of two electrons, conformation 1B may be converted into the cis β-carbanionic species 10 with a minimum amount of motion of atoms and solvent-shell reorganization.



1A ⇌ 1B

The magnitude of the change in the stereochemistry of the reduction with the change in metal cation is small but outside the range of experimental error. The results show that within the alkali metal and alkaline-earth metal series the smaller cations, i.e., Li^{+} and Ca^{+2}, respectively, yield less of the cis-fused product 4 than the larger cations. At first sight this is surprising since the β-carbanion-metal complex seems to be in a slightly more crowded environment in configuration 10 than 9. Also, since the charge is more localized at the β-position in 10 a closer approach of the metal to the carbanionic center might be expected to be necessary in this case. However, the literature contains a number of suggestions that the smaller metal cations are more extensively solvated by ammonia than larger cations.[3c] If the metal-ammonia complex is actually larger for the smaller than for the larger metal cations, this could account for the greater amounts of trans product obtained in the reductions using lithium and calcium. Also, if the species undergoing β-protonation is a dianion rather than a hydroxy allyl anion it might be expected that 9 would be stabilized relative to 10 when metal cations such as Li^{+} and Ca^{+2} are involved. These cations should form more covalent bonds with the oxygen atom than the more electropositive metal cations thus allowing more favorable overlap of the β-carbanion with the π electron system of the metal enolate.

Experimental Section[11]

General Procedure for the Metal-Ammonia Reduction of Octalone 1.[3c]

Anhydrous liquid ammonia (300 ml, distilled from sodium) was distilled under nitrogen into a flame-dried three-necked flask fitted with a mechanical stirrer, an addition funnel, and a Claisen adaptor holding a dry-ice condenser and a gas inlet tube. Freshly cut metal, 0.022 g.at. of alkali metal or 0.011 g.at. of the alkaline-earth metal, was then added and the mixture was stirred until the metal had completely dissolved (15-45 min). A mixture of 1.78 g(0.010 mol) of octalone 1 and 0.74 g(0.010 mol) of tert-butyl alcohol in 70 ml of anhydrous ether (distilled from $LiAlH_4$) was added dropwise with stirring over 30 min at -33°. Stirring was continued for 3 h and then 3.14 g of solid ammonium chloride was added as rapidly as possible. The ammonia was allowed to evaporate and the residue was dissolved in 200 ml of a 1:1 ether-water mixture. The layers were separated and the aqueous layer was saturated with sodium chloride and extracted with three 50-ml portions of ether. The ethereal extracts were combined and dried over magnesium sulfate. After removal of the solvent *in vacuo* the residue was analyzed by GLC and distilled to give a mixture of decalones 3 and 4 in the yields given in Table I.

Pure samples of ketones 3 and 4 were collected by preparative GLC. Ketone 3 showed identical IR, ^1H NMR, and mass spectral properties and GLC behavior to an authentic sample.[4] Its ^{13}C chemical shifts are recorded in Table I. Compound 4 showed: mp 51.0-52.0°; IR(CCl_4) 1711, 1460, 1442, 1379, 1330, 1305, 1157, 1142, and 1110 cm^{-1}; NMR(CCl_4) δ 0.89 (d, 3H, J = 3.8 Hz) and 1.25 ppm (s, 3H); MS (70 eV) *m/e* 180(28) and 109(100).

Anal. Calc for $C_{12}H_{20}O$: C, 79.94; H, 11.19. Found: C, 79.85; H, 11.18.

The ^{13}C chemical shifts of 4 are recorded in Table I. It formed a semicarbazone, mp 182.0-183.0.

Anal. Calc for $C_{13}H_{20}N_3O$: C, 65.79; H, 9.77; Found: C, 65.70; H, 9.81.

Preparation of Ketone 6. Ketone 6 was prepared in ~90% yield by lithium-ammonia reduction of the enone 5 according to the general procedure described for the enone 1. Ketone 6 (bp 110-112°/0.1 mm (lit[4b] 80°/0.01 mm)) showed identical IR, ^1H NMR, and mass spectral properties to those reported for the optically active matieral.[4b] It formed a semicarbazone: mp 203-204° (lit.[7] mp 202.5-203.0°). The ^{13}C chemical shifts are shown in Table I.

Catalytic Hydrogenation of Enone 1. To a solution of 0.32 g of octalone 1 in 6 ml of 95% ethanol was added 0.056 g of 10% palladium-on-carbon. The mixture was hydrogenated in a Parr apparatus for 2 h at 35 psi hydrogen pressure. Removal of the catalyst by filtration and removal of the solvent *in vacuo* gave a mixture of decalones 3 and 4 (bp 110-115°(bath temperature)/0.1 mm) in essentially quantitative yield. Analysis of the mixture by GLC showed that it contained ~65% 3 and ~35% 4. A trace (<3%) of decalone 6 was also present.[5]

Catalytic Hydrogenation of Enone 5 in Acidic Medium. To a solution prepared from 0.80 g of octalone 5, 1.5 ml of 3.2 N hydrochloric acid, and 15 ml of 95% ethanol was added 0.15 g of 5% palladium-on-carbon. The mixture was hydrogenated in a Parr apparatus for 2 h at 35 psi hydrogen pressure. On removal of the catalyst by filtration and removal of the solvent *in vacuo*, GLC analysis of the residue showed that it was composed of a 5:95

mixture of decalones $\underset{\sim}{6}$ and $\underset{\sim}{7}$. Distillation of the mxiture under reduced pressure gave 0.403 g (49%) of pure $\underset{\sim}{7}$: bp 108-112°/0.10 mm; IR (film) 1713, 1462, 1447, 1430, 1379, 1355, 1340, 1284, 1266, 1243, 1217, 1185, 1155, 1133, 1109, 1072, 1022, 1005, 934, 826, and 755 cm^{-1}; NMR (CCl_4) δ 0.81 (d, 3H, J = 6.6 Hz) and 1.06 ppm (s, 3H); MS (70 eV) m/e 180 (37), 109 (100), 108 (88), 95 (65), 81 (53), 67 (54), 55 (84), and 41 (79); semicarbazone mp 202.0-203.0°(lit.[7] 202.2-202.5°).

References and Notes

1. This investigation was supported by Grant No. CA12193, awarded by the National Cancer Institute, DHEW. The research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

2. D. Caine, A. A. Boucugnani, and W. R. Pennington, J. Org. Chem., 41, 3632 (1976).

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4. a. The major reduction product 3 showed identical nmr, ir, and mass spectral properties and chromatographic behavior to an authentic sample of racemic 3 which had identical spectral and chromatographic properties to the optically active material obtained by oxidative degradation of dihydroeudesmanol (ref. 4b). We are grateful to Dr. B. Maurer for providing us with a generous supply of authentic racemic 3. b. B. Maurer, M. Fracheboud, A. Grieder, and G. Ohloff, Helv. Chim. Acta., 55, 2371 (1972).

5. A trace (<3%) of the decalone 6 was obtained in the catalytic reduction of 1. This product may have arisen because 1 was slightly contaminated with the trans isomer 5 or a slight amount of isomerization of 1 into 5 may have occurred under the reaction conditions.

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11. Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. The ^{1}H NMR spectra were obtained on a Varian T-60 NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (ppm) to TMS as an internal standard. The mass spectra were

obtained with a Hitachi(Perkin-Elmer) Model RMU-7. Gas-liquid chromatography was carried out using a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. A 6 ft. x 0.125 in. aluminum column packed with 20% Carbowax K-20M on acid washed chromosorb W was employed for analytical work and a 10 ft. x 0.25 in. stainless steel column containing the same packing material was used for preparative work. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, Georgia.

GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GEORGIA 30332

OFFICE OF
THE DIRECTOR OF
FINANCIAL AFFAIRS

September 28, 1977

National Cancer Institute
Grants Administration Branch, DCRRC
Room 840, Westwood Bldg.
Bethesda, Md., 20014

Gentlemen:

Enclosed is the final Report of Research Grant Expenditures for Grant Number 5 ROI CA12193-09 covering the period May 1, 1976 through April 30, 1977.

If you have questions or desire additional information, please let us know.

Sincerely yours,

Evan Crosby
Associate Director of
Financial Affairs

EC/bs
Enclosure:
cc: Dr. J. A. Bertrand
Dr. D. S. Caine
Mr. E. E. Renfro
Mr. A. H. Becker
File G-33-612

☆U.S. GOVERNMENT PRINTING OFFICE: 1976-721-809

Department of Health, Education, and Welfare

NAME AND ADDRESS OF GRANTEE INSTITUTION	TRANSACTION NO.	Grant No.
Georgia Institute of Technology Atlanta, Georgia 30332	(08)R1CA12193A INSTITUTIONAL ID NO. G-33-612	5-ROI CA12193-09 DATE OF THIS REPORTING PERIOD FROM 5/1/76 TO 4/30/77 PROJECT PERIOD FROM 5/1/74 TO 4/30/77 ☒ CHECK IF FINAL REPORT

1. Expenditures of DHEW Funds for this Reporting Period

a. Personnel	$ 27,997.10	h. Alterations and renovations	
b. Consultant services	325.00	i. Other	
c. Equipment			
d. Supplies	4,447.56	j. Total direct costs	33,257.02
e. Travel, domestic	487.36	k. Indirect costs: Rate 68 % ☐ S&W ☐ TDC	
f. Travel, foreign		Base $ 27,437.44	18,657.46
g. Patient care costs		l. TOTAL	$ 51,914.48

2. Expenditures from Prior Periods (previously reported)	96,111.00
3. Cumulative Expenditures	148,025.48
4. Total Amount Awarded — Cumulatively	148,212.00
5. Unexpended Balance (Item 4 less Item 3)	186.52
6. Unliquidated Obligations	-0-
7. Unobligated Balance (Item 5 less Item 6)	186.52
8.a. Cost Sharing Information — Grantee Contribution This Period	5,445.83
b. % of Total Project Costs (Item 8a divided by total of Items 1 and 8a)	% 9.5
9.a. Interest/Income (enclose check)	
b. Other Refundable Income (enclose check)	

10. Remarks

I hereby certify that this report is true and correct to the best of my knowledge, and that all expenditures reported herein have been made in accordance with appropriate grant policies and for the purposes set forth in the application and award documents.

Project Director

Associate Dir. of Fin. Affairs — September 26, 1977

SIGNATURE OF INSTITUTION OFFICER — 404-894-4622 — DATE

HEW-489 (REV. 10/73)

REPORT OF RESEARCH GRANT EXPENDITURES

OMB 85R0219